OSTEOGENESIS IMPERFECTA IN SWEDEN

CLINICAL, GENETIC, EPIDEMIOLOGICAL AND SOCIO-MEDICAL ASPECTS

BY

Gunnar Smårs

THE SECTION ON SOCIO-MEDICAL ASPECTS
WRITTEN TOGETHER WIHT *Ragnar Berfenstam*

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PREFACE

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The clinical part of the work has been furthered by my former chief, professor Erik Ask-Upmark, head of the Division of Internal Medicine of the University Hospital of Uppsala, to whom I feel much indebted.

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Gunnar Smårs

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I Introduction

Osteogenesis imperfecta is a rare genetic disease. The most prominent symptom is a more or less pronounced fragility of the bones. In the majority of cases the sclerae have an abnormal, blue tint. An impaired hearing is frequent and many of the affected have an increased extensibility of the joints (hyperlaxibility). It is thought that these manifestations originate from defects in the primary elements of the mesenchymal tissue.

The disease has not often been subjected to systematic investigations. This is probably due to its rarity and hence the difficulty in obtaining sufficient study material. There are, however, numerous casuistic reports which often picture single and probably the most unique cases.

In order to assess a disease as accurately as possible from different angles of approach, it is necessary to have access to a systematically collected and uniformly evaluated material. Apparently, Seedorff (1949) is the only previous author who collected such a material of osteogenesis imperfecta.

This investigation started with two patients, a mother and her child, who were admitted to the medical and pediatric departments from the obstetric unit of the University Hospital, Uppsala in April—May, 1951. Various questions concerning the disease arose out of an investigation of these two patients, e. g. its frequency, clinical course, prognosis and therapy, and also concerning the possibility of preventive measures, the influence of pregnancy and other factors upon the severity of the symptoms, and finally various socio-medical problems. Only incomplete information was available in the earlier literature (cf. Berfenstam and Smårs, 1956).

The present material was collected in order to fill some of the gaps in the knowledge of this disease. This investigation has been limited to deal with the following aspects of the disease:

1. The signs and symptoms assessed by a systematically collected and uniformly examined material.
2. The frequency and distribution in Sweden and the genetic behaviour.
3. The socio-medical significance.

An original material of 274 cases of osteogenesis imperfecta will be reported. Of this total 190 cases were subjected to a detailed personal inquiry. Together with 22 cases who died early in life, and for whom case histories were received from various hospitals, these 190 cases provided a basis for a clinical study. The genetic and epidemiological analysis is based for the main part upon the total material.

In collaboration with R. Berfenstam a special socio-medical analysis was made of the 190 individuals who were subjected to personal interviews and examinations. These results are reported in the last section of this work.

II. Review of the literature and history

Hereditary fragility of the bones was first described by O. J. Ekman. In 1788 he described, in a treatise published in Uppsala, a family from Dannemora in Uppland in Sweden, in which seven members in four generations showed severe deformities due to abnormal osseous fragility with repeated fractures. Ekman named the affection congenital osteomalacia. According to the parish registers the family finally became extinct on the death of the last member of the family who was still alive at the time of Ekman's study. Ekman's treatise, translated from Latin into English, may be found in Seedorff's study (1949).

Solitary cases of fragile bones with multiple fractures and deformities are reported from about the year 1700 (cf. Griffith 1896, Seedorff 1949).

In 1831 E. Axmann, who himself together with two younger brothers had the disease, gave a very clear description of bone fragility in connection with blue sclerotics, hyperlaxibility with tendency to articular dislocations and a slender body constitution. He referred to these traits as an expression of a weakness of the fibrous tissues. His description of the syndrome does not leave much to be desired. The following is cited:

"Obgleich als gesunde Kinder geboren trugen dennoch meine beiden jüngeren Brüder sowohl, als ich, das Gepräge einer schwächlichen Organisation. Vorzüglich zeigte sich diese Schwächlichkeit im Knochenbau und in den fibrösen Gebilden. Sämmtliche, besonders aber die Röhrenknochen waren auffallend dünn und schwach, und die Ligamente aller Artikulationen so ungemein schlaff und nachgiebig, dass die Bewegungsfähigkeit der miteinander verbundenen Gelenktheile weit über die gewöhnliche Grenze ausgedehnt werden konnte, wodurch aber auch zugleich zu häufigen Verrenkungen und Verstauchungen Gelegenheit gegeben war. Diese Zartheit der Organisation des Fasersystems trat ausserdem noch besonders auffallend im Auge hervor. Die Sclerotica ist nämlich bei allen Brüdern so ungemein dünn und zart, dass die darunter liegende Chorioidea durchschimmert, wodurch dass Weisse des Auges eine tiefblaue

Färbung erhält, die ganz derjenigen gleicht, die wir bei variköser Metamorphose gichtkranker Augen beobachten, was der verstorbene Beer in Wien, wessen Vorlesungen ich im Jahre 1811 besuchte, als eine früher in diesem Grade von ihm nie beobachtete Eigenthümlichkeit der Bildung erkannte."

Axmann also stated that both his parents were healthy from youth to old age, and did not reveal any signs of bone fragility or weakness of the fibrous tissues described. Only a slight scoliosis in the lumbar region could be noticed in his mother. Although Axmann was later cited by several authors (among others Guilt 1862, Griffith 1896, Bronson 1917) they apparently only noted his description of the bone fragility. Hence Spurway (1896) and Eddowes (1900) (see below) until quite recently were considered to have been the first to have noticed blue sclerotics in connection with the disease. Caniggia et al. (1958) seem to have been the first to point out Axmann's early description of blue sclerotics and hyperlaxibility as a part of this syndrome.

In 1833 Lobstein of Strassburg also described hereditary bone fragility and coined the name osteopsathyrosis idiopathica. The condition has been named after him "Lobstein's disease".

In 1849 Vrolik described a child who died at the age of three days. The head was large, and the bones of the skull were found to be composed of a great number of smaller irregular ones, Wormian bones. The extremities and ribs showed multiple fractures. Following Vrolik's description this early manifested severe form, which was long considered a disease per se, was called either "osteogenesis imperfecta" or "Vrolik's disease". Stilling (1889) showed histologically that the disorder was not due to any form of rachitis, as was assumed up till then.

The similarity between osteogenesis imperfecta (Vrolik) and osteopsathyrosis idiopathica (Lobstein) was noted already in 1899 by M. B. Schmidt. In 1906 Looser on the basis of striking histological similarities between the two forms concluded that they were identical. This histological identity was later verified by other investigators (Bauer 1920, Knaggs 1924, Heise 1932 and others). The opinion that these two disease entities are an expression of one and the same disturbance, although of different severity, has gradually gained more ground and is now generally accepted. Looser's suggestion that the name osteogenesis imperfecta congenita be used for the form described by Vrolik, and osteogenesis imperfecta tarda for that described by Lobstein has been increasingly accepted. (Cf. section on Terminology.)

In 1896 Spurway described a family with a hereditary tendency to fractures, and writes that "the only other feature I have noticed common to many members of this family is a curious bluish tinge of the eyeball, which in some is very marked". As already mentioned this was for some long time considered to be the first documented description of blue sclerotics in connection with brittle bones until Caniggia et al. (1958) drew attention to Axmann's description.

In 1900 Eddowes called attention to the combination of brittle bones with blue sclerae. He also, like Axmann, suggested a mesenchymal deficiency ("want of quantity or quality of the fibrous tissue forming the framework of the various organs of the body") as an explanation for both the bone fragility and the blue sclerae, a hypothesis which in 1920 was again taken up and further developed by K. H. Bauer. The latter claimed the presence of an abnormal structure not only within the osseous tissue but also in the dentine and the connective tissues of the skin. Similar findings have been described later by other authors (R. H. Follis 1953, Ruedemann 1953, Bergman-Engfeldt 1954).

Impaired hearing in connection with blue sclerae and brittle bones seems to have been noted first by Adair-Dighton, who in 1912 in a report of a family with these latter symptoms also mentions a 23 year old woman who 3 months post partum became hard of hearing. In 1917 Bronson observed early deafness in seven out of eight adult cases within one family with blue sclerae. Deafness was definitely incorporated in the syndrome together with blue sclerae and brittle bones by van der Hoeve and de Kleyn (1918). The syndrome idiopathic bone fragility — heredity — blue sclerae — deafness has since often been called van der Hoeve's syndrome.

An increased flexibility of the joints, hyperlaxibility, which often causes distortions and dislocations has been emphasized as a common symptom by several authors (Behr 1913, Bronson 1917, Gutzeit 1922, H. Nielsen 1942). As mentioned above the symptom had already been noticed by Axmann (1831).

Not until after about 1920 was any particularly large material of osteogenesis imperfecta collected. The publications up to that time mostly concern single cases or families.

J. A. Key (1926) gave a summary of the most important families with blue sclerae and brittle bones described since Spurway's publication in 1896. This summary comprised a total of 241 affected individuals.

In 1928 J. Bell reported 463 hereditary cases of blue sclerae divided into 73 families, which had been described in the literature since 1903. In 252 of these cases there was information suggesting that they had had one or several fractures, and in 98 cases that they had suffered from deafness.

A still larger material from the literature was published in 1935 by H. Fuss. It comprised a total of 89 families with approximately 1000 members with 515 cases of hereditary osteopsathyrosis.

However valuable such compilations from the literature might be, they still show some grave imperfections both in regard to the assessment of the clinical picture and to the genetic analysis. There are for example no uniform evaluating standards and the collecting of the material is not free from selection, which inevitably results in serious biases.

In 1949 K. Seedorff published an investigation from Denmark comprising 55 families with 180 persons suffering from osteogenesis imperfecta. Of these he personally examined 60 cases. For another 28 there were hospital reports and for 90 others he apparently had information from relatives or other people. This material, besides being investigated and evaluated uniformly, seems also to a great extent to comply with the demand for an unbiased collection, in that the author used for his study probands registered at The University Institute for Human Genetics in Copenhagen.

Seedorff concluded as a result of his investigation that "osteogenesis imperfecta is a hereditary disease, presenting complete, autosomal dominance, and due in all its types to mutation". His material did not permit an estimation of the mutation frequency.

Regarding the different signs and symptoms Seedorff found frequency numbers that partly agreed with and partly differed from those of earlier authors.

Following Seedorff's monograph in 1949 the literature on osteogenesis imperfecta has grown considerably. In 1956 Komai, Kunii and Ozaki described a Japanese family including 106 cases of the disease and presented a genetical analysis of the material. They also attempted to estimate the gene and mutation frequency of the disease. Apart from this work the literature consists of casuistic contributions illustrating the disease, histopathological studies (among these Follis 1952 and Engfeldt, Engström and Zetterström 1952) and general articles (among these McKusick 1956 and Berfenstam and Smårs 1956). An extensive

bibliography is to be found in a monograph published in 1958 by Caniggia, Stuart and Guideri, who, on the basis of four carefully studied families with a total of 23 cases of osteogenesis imperfecta, describe the disease from a clinical, roentgenological, anatomical, histological and genetic point of view.

Summarizing the survey of the literature of osteogenesis imperfecta I would stress the following:

1. The literature on osteogenesis imperfecta is extensive, and seems to have shed light upon the disease from most angles.

2. The hereditary nature of the disease has been shown in a great number of the cases which have survived. Autosomal dominant heredity seems to be present. Sporadic cases are considered as possibly due to mutations.

3. An immature irregular structure of the osseous tissue with a disturbed function of osteoblasts has been demonstrated histologically as a cause of the bone fragility. Bone rebuilding is greatly deficient. The formation of the matrix is defective with sparse and abnormally organized collagen. Similar changes have been demonstrated in the dentine; further, some authors claim to have found such changes in the skin, sclerae and corneae. This has prompted the supposition that this disturbance in all its different aspects originates in some general defect in the embryonic mesenchymal tissues. The biochemical basis of this disturbance remains to be explained.

4. Even though numerous publications have illustrated the disease from almost all conceivable points of view the clinical and genetic pictures have been largely derived from reports of a casuistic nature. Seedorff (1949) alone has published in a monograph a more representative material as a basis for a clinical and genetic analysis. Many questions remain unanswered regarding the clinical picture, epidemiology and genetics, as well as the socio-medical importance of this disease, thus warranting a further study along these lines.

III. Terminology

As has been mentioned in the literature survey, Looser's (1906) suggestion of a nomenclature for the disease has been generally accepted. Looser's suggestion implied that the name osteogenesis imperfecta which earlier had been reserved for the severe form described by Vrolik, should be extended to designate also those cases of the disease which Lobstein had called osteopsathyrosis idiopathica. If for practical reasons it should be considered necessary to make a difference between the two forms, Looser suggested that the distinction be made between:

osteogenesis imperfecta congenita and
osteogenesis imperfecta tarda.

By osteogenesis imperfecta congenita Looser obviously meant such cases that complied with Vrolik's definition of osteogenesis imperfecta, namely osseous fragility, causing fractures and deformities already prior to birth. The frequently occurring defective ossification of the skull was also mentioned. Up to the time of Looser this condition seems to have been observed only in cases so severe that they either died prior to birth or lived at the most a few weeks or months after birth.

By osteogenesis imperfecta tarda Looser meant the more moderate form of brittle bones (earlier called osteopsathyrosis idiopathica), which reveals itself by fractures appearing some time after birth, sometimes not until many years later, and which is well compatible with life.

In view of the fact that all conceivable transitions may be found between the so called congenital cases and those which manifest themselves by fractures later in childhood, Looser strongly doubted that such a classification was appropriate. He held the opinion, however, that a division into two groups might be of a certain practical value in order to differentiate between the extreme cases, which appear to be clinically very different.

Looser also raised the question of whether those cases which he designated "tarda" should not really be considered as congenital, differing from the more severe congenital cases only in the mildness of their form, their manifestations appearing later.

Later authors do not seem to have borne in mind this reasoning of Looser's. They have, however, considered Looser's practical suggestion, presented with some hesitation, that one might possibly still differentiate between two forms of the disease, namely, on the one hand, osteogenesis imperfecta congenita (called Vrolik's disease by some) and, on the other hand, osteogenesis imperfecta tarda. The latter form was earlier designated as "osteopsathyrosis idiopathica", "Lobstein's disease", "fragilitas osseum", "van der Hoeve's syndrome" and by several other names. This has caused a marked confusion in the terminology.

Seedorff in his monograph of 1949 used Looser's nomenclature, but suggested a further division into types, namely:

Type I: osteogenesis imperfecta congenita
Type II: osteogenesis imperfecta tarda g r a v i s
Type III: osteogenesis imperfecta tarda l e v i s.

Even though Seedorff stressed at several points the uniformity of the disease and pointed out that there were no sharp lines of distinction between the different groups, such a classification easily gives the impression that there are different disease entities, not merely different degrees of severity of the same disease. This impression is strengthened by the classification of different names for the disease as, for instance, in Cecils Textbook of Medicine (10:th ed., 1960).

I. Osteogenesis imperfecta, Vrolik's disease, osteopsathyrosis congenita (Looser).
II. Osteopsathyrosis, idiopathic osteopsathyrosis, Lobstein's disease, osteopsathyrosis tarda (Looser).
III. Brittle bones and blue sclerae, Spurway's disease, hereditary hypoplasia of the mesenchyme (Key).

Such a classification might be justified as an attempt at bringing together the terminologies of different authors as they apply to different degrees of severity of the disease. Unfortunately, however, it might easily create the false impression that the different names represent more or less clearly distinct forms of the disease.

There seem to be no valid reasons for assuming that there are different types of the disease. Many writers since the time of Looser have, as mentioned, shown that the histological picture is identical in the different degrees of severity.

Several authors since Looser have published cases which verified his assumption that the so called tardive cases are in fact congenital ones, that is that they show manifestations of the disease both prior to and at birth. Among such cases may be included those described in 1913 by Zurhelle, in 1926 by Rosenbaum and in 1929 by Puppel. These cases showed at birth fractures incurred in utero as well as disturbed ossification of the cranial bones. According to earlier definitions of osteogenesis imperfecta (Vrolik) and osteopsathyrosis idiopathica (Lobstein), these would be regarded as belonging to the former variety of the disease in spite of the fact that the children, to judge by the description, were quite fit to survive. As the mothers in each of these three cases had had brittle bones with fractures from early childhood, they were considered as examples of inherited cases of congenital osteogenesis imperfecta. Zurhelle was of the opinion that his cases supported Looser's view that osteopsathyrosis idiopathica (Lobstein) and osteogenesis imperfecta (Vrolik) were one and the same disease, which should be called osteogenesis imperfecta. Looser's suggestion that the disease be divided into a congenital and a tardive form was, however, rejected by Zurhelle who argued that the so called late forms can obviously be traced back to congenital changes.

Seedorff's family No. 7 should also be included in the same category as the three last mentioned cases. The mother in this family, who had bilateral femoral fractures at birth, survived, later to develop severe deformities. The child showed multiple fractures at birth and typical caput membranaceum with large fontanelles, wide sutures and soft cranial bones. The child died 6 months later. Seedorff indicates the mother as a case of osteogenesis imperfecta tarda and the child as a typical case of osteogenesis imperfecta congenita.

Looft (1911) described what he considered to be a typical congenital case of osteogenesis imperfecta with fractures and deformities in utero but which survived and was still living at the age of 5 1/2 years. Bamberg and Huldschinsky (1913) described a case which according to the criteria recognized at that time was also regarded as belonging to the congenital form of the disease, but was still alive at the age of 3 years. Schabad (1914) described a similar case alive at 10 years of age. In referring to these three cases Seedorff writes: "However, it is a question whether these cases should not actually be regarded as belonging to the tardive form of the disease, since, as will later be pointed out, there are no sharp lines of distinction between the different types or forms." Seedorff himself in an earlier section on terminology wrote: "Generally the term osteogenesis imperfecta (Vrolik) is used in the literature for the form of the disease where the patients are born with multiple fractures, partly of intrauterine origin, and partly incurred sub partum, as well as failing of the bones of the calvaria. The late or tardive form of the disease, where the liability to fractures manifests itself shortly after birth or later, is generally termed osteopsathyrosis idiopathica (Lobstein)."

Seedorff appears to a great extent to have used these definitions. Contrary to the authors referred to above who, among others, described so-called surviving congenital cases, Seedorff has attempted to modify the definition of con-

genital cases (osteogenesis imperfecta congenita), restricting them to the non-surviving cases of this group. In Seedorff's material the longest survival of a case designated osteogenesis imperfecta congenita was 15 months.

A detailed study of the terminology and definitions of this disease thus shows that it is impossible to distinguish clearly between a congenital and a tardive form. In attempting to apply the previously generally accepted criteria of osteogenesis imperfecta congenita, namely, that fractures and faulty ossification must be present prior to birth, it is found that cases capable of survival should also be considered as belonging to this group. If a thorough examination were carried out at birth, it is probable that disturbances of bone formation could be demonstrated at this time in many cases later placed in the "tardive" group. If, however, the previously generally accepted definition of osteogenesis imperfecta congenita is modified, and thus only used for describing those cases which due to the disease do not live longer than, say, a few months or at most 1 or 2 years, there would then no longer be any reason for the designations "congenita" and "tarda". It would thus be more natural, as in the case of an acute infectious disease, for instance poliomyelitis, to refer to the disease as having a lethal, severe, mild or abortive course.

I will briefly relate a few cases from my own material which have made it necessary for me to take up the question of terminology, and to state my opinion. In the case of one girl (case No. 135:1, cf. p. 53) there are detailed reports in the hospital records showing that she already had at birth multiple bone fractures of the extremities, with deformities. X-ray examination showed formation of callus. The skull felt membranous. The sclerae were bluish gray. The case was considered to be one of osteogenesis imperfecta congenita with poor prognosis. Yet at the age of 5 years the patient was still living and in good general condition. She had had 24 fractures and was not able to walk by herself but moved about using a walking chair. This patient appears to have a good chance of living and to enter into a more quiescent phase of the disease. In the case of another girl (case No. 146:1, cf. p. 229) there were definite reports of the skull being soft at birth, when blue sclerae were also noticed. Between the age of 8 months and 4 years she had had 5 fractures. When 9 years old she was examined and found to be fully active and attending school, but showing a certain degree of deformity of the spine and the right femur. In the case of a 30 year old man (No. 168:3, cf. p. 230), who had a total of more than 20 fractures and whose back and extremities were severely deformed, there were distinct reports of the skull being as soft as a rubber ball at birth. Among the parents and other relatives of these three cases there were no signs of skeletal disease.

A boy who was 6 years old when the field examination was carried out has been followed up from birth (case No. 10:1, cf. p. 100). At birth there was an unmistakable derangement of the ossification within the cranial bones typical of osteogenesis imperfecta and demonstrable by palpation and X-ray examination. In addition he showed blue sclerae and hyperlaxibility combined with a moderately faulty position of one foot. Since then he has had only a few minor fractures and has developed normally except for a troublesome pes planocalcaneo-valgus. He belongs to a family with moderately severe osteogenesis imperfecta, known for five generations. A girl (No. 43:1, cf. p. 223) who was 7 years old at the time of the field examination, had bilateral fractures of the femora, disturbed ossification of the skull and blue sclerae at birth. Except for two later fractures she has developed normally and moves about freely. When her younger sister (No. 43:2) was examined at the age of 6 months, roentgen examination likewise showed residual signs of previously non-observed bilateral femoral fractures and deranged ossification of the skull. The father and a maternal aunt of these last two cases also showed obvious signs of the disease, and the maternal grandmother had had blue sclerae and a disposition towards fractures.

Each one of these six cases should be considered as congenital in the strict sense. Clinically, however, they do not differ in any respect from cases which in the literature are designated osteogenesis imperfecta tarda, osteopsathyrosis idiopathica or by other synonyms.

As there is no longer any valid reason, either histologically or clinically, for dividing osteogenesis imperfecta into a congenital and a tardive form, I have considered it best to avoid such a classification in presenting this material, and to regard the disease as an entity, osteogenesis imperfecta, of different degrees of severity.

In describing the different degrees of severity I have primarily attempted to differentiate between non-surviving (lethal) and surviving cases. In describing the surviving cases they are grouped according to severity as assessed by the degree of impaired mobility.

As it is impractical to free oneself entirely from the earlier terminology, it is used to a certain extent in this study when, for instance, referring to the literature. In so doing I have aimed at preserving the meaning of these terms as used by Looser, and later Seedorff, namely, that osteogenesis imperfecta congenita designates *non-surviving* and osteogenesis imperfecta tarda *surviving* forms of the disease, irrespective of whether the manifestations of the disease are established before or after birth.

In view of the uniformity of the histological and clinical picture, I

have tried to avoid a terminology which postulates the existence of different types of the disease. On the other hand, I have not inferred any opinion as to whether or not the disease is a genetic entity. I am conscious of the possibility that one and the same phenotype may be due to different genotypes, that is that one trait or disease in one case may be traced to one gene, and in another case to one or more other genes, or that it might depend on other factors. This problem will be discussed later in the genetic analysis of the material.

From a practical, clinical point of view the terminology in certain cases is quite important. This is particularly so when, for example, clear signs of osteogenesis imperfecta can be established in a child at birth, e. g. in the form of one or more fractures. If this case is then diagnosed as osteogenesis imperfecta congenita, with the resulting poor prognosis which this diagnosis implies according to the earlier literature, the case may easily be misjudged. This might influence the doctor's treatment as well as the parents' attitude towards the child. The same holds true even for those cases which later in life experience more or less severe bouts of the disease.

IV. Diagnostic criteria

In earlier literature osteogenesis imperfecta is described as a syndrome, characterized, in the main, by idiopathic osseous fragility, blue sclerae, impaired hearing and hyperlaxibility. The last two characteristics are regarded as symptoms of second order which, taken alone, are not sufficient for establishing a diagnosis. A strict diagnosis requires the presence of the two first mentioned symptoms, brittle bones and blue sclerae.

As implied earlier different degrees of severity will be encountered in this as in other diseases. Previous authors (Bell 1928, Seedorff 1949) have stressed the fact that the severity of the osseous fragility and the intensity of the blue tinge in the sclerae are independent of one another. If one of the symptoms is less clearly manifested, the other may help to establish the diagnosis. In such cases, however, specific criteria are required.

An important question is whether or not the diagnosis of osteogenesis imperfecta can be established by the presence of only one or the other of the two main symptoms. Judging from the literature the question of whether idiopathic osseous fragility alone is sufficient for making a diagnosis is not settled.

Key (1926) seems to have considered idiopathic brittle bones without blue sclerae, but he held the opinion that this was a disease entity different from the one combining brittle bones and blue sclerae.

Bell (1928) noted that women predominated (54.4 %) in a group of 237 cases showing both brittle bones and blue sclerae, while there was a higher frequency in men (68.8 %) in a material consisting of 96 cases with brittle bones and no blue sclerae. Until a larger material was collected she did not therefore consider material comprising only brittle bones, and material combining brittle bones and blue sclerae to be homogeneous.

Fuss (1935) collected 392 cases of hereditary osteopsathyrosis and

found that 370, i. e. 94.4 % were noted to have had blue sclerae. He stated "dass Knochenbrüchigkeit fast nur bei vorhandenen blauen Skleren auftritt".

Seedorff (1949) seems to think that every person with a disposition for the disease has blue sclerae. He states, however, that "a few writers (Key, Holcomb, Asplund) have reported cases of idiopathic bone fragility which were not attended by blue sclerotics", but then adds: "This is, however, no doubt due to a failing experience in estimating the colour qualitatively, as well as the fact that where the sclerotics are not particularly thin, so that the blue tinge becomes faint only, the colour of the sclerotic will seem strikingly white." In his own material Seedorff maintained that every case, both isolated ones and those appearing together within the same family, had blue sclerae.

Among the writers quoted above it is thus evident that Key and Bell, from a review of the literature, are of the opinion that there do exist hereditary cases of idiopathic bone fragility without blue sclerae. However, they are inclined to classify these cases into a separate group, different from that with a combination of brittle bones and blue sclerae. On the other hand, Seedorff, who has collected the largest number of cases, is of the opinion that blue sclerae are always found with hereditary idiopathic osseous fragility.

In collecting the present material I inquired after cases showing definite or probable signs of osteogenesis imperfecta. In the primary material received as a result of this inquiry there are 16 solitary cases and five (5) families comprising 14 cases with idiopathic brittle bones, which when examined showed normal colour of the sclerae. It is difficult to estimate to what extent the physicians questioned may have failed to report other similar cases because of the absence of blue sclerae. (Cf the section on "The completeness of the material".) The cases mentioned have been examined and the information considered together with the rest of the material. As these cases, as regards osseous fragility, the development of fractures at certain ages, and the appearance of the deformities are identical with those showing both idiopathic brittle bones and blue sclerae, I have considered it justifiable to include this group when studying and assessing the rest of the material of osteogenesis imperfecta. In support of this unitary concept, a family may be mentioned (no. 97 in the material) in which there are four (4) children with idiopathic bone fragility, of whom two have markedly blue sclerae,

while the other two have not. A comparison of the two groups will be made in the section on genetics.

In cases of idiopathic osseous fragility without concomitant blue sclerae, in which the diagnosis is thus suggested only by the tendency towards fractures, it has been necessary to define more clearly the criteria of this sole manifestation of the disease.

For example: in one family (family No. 35, cf. p. 32), both the father and one of the sons have had repeated fractures with no significant trauma, thus warranting the diagnosis even in the absence of blue sclerae. No other reasons for the osseous fragility have been found. Another son likewise has had two fractures, once through falling on ice, once through a fall when jumping. It is possible that these fractures were due to a certain degree to osseous fragility, but as trauma existed on both occasions, and is in itself sufficient for explaining the presence of the fractures, and as other signs of the disease were lacking, this case was considered uncertain and was excluded from the material in spite of the positive heredity.

Thus, osseous fragility alone has been considered adequate for the diagnosis only when a patient has repeated fractures without there being concomitant causative factors.

When using the expression "blue sclerae" it is necessary to attempt to distinguish clearly between blue and normal sclerotics. As Seedorff and several earlier writers have stressed, the blue tinge may show different grades of intensity. This is evident from the following descriptions: "blackish blue" (Bell), "marineblaue Tönung" (Hirschman), "very blue" (Casanovas), "slate blue" (Curtin), "a mere bluish tinge, similar to that seen normally in a newborn child" (Bell). As variations in the colour of the sclerae are normally found, with more or less marked blue shadings, it is often difficult to distinguish between the normal and the abnormal. A fairly objective estimate would be possible by using a colour-chart, were it not that the scleral colour is not homogeneous but often varies in different zones. Thus the colour-chart would hardly be of any help in doubtful cases. Through experience with normal cases the author has tried to develop a sense for differences of shade in the scleral colouring and upon this basis has judged the different cases. When in doubt the patient's sclerae have been compared with those of healthy members of the family or of other persons present at the time of the examination.

The presence of blue sclerae has in itself been considered strong

evidence of the diagnosis of osteogenesis imperfecta. In assessing the probands, i. e. the patients serving as starting points for the investigation, I have established the criterion that they also show osseous fragility demonstrated by one or several fractures produced without adequate cause. Relatives of the probands have, however, been regarded as affected when presenting abnormally blue sclerae even without demonstrable osseous fragility.

A family which, judged by these criteria, could not be included in the material may be taken as an illustration. A girl, seventeen years old, was admitted to hospital because of slight joint trouble and was found to have abnormally blue sclerae and hyperlaxibility. In the inquiry she was reported as a suspected case of osteogenesis imperfecta. When examining the family it was found that the father (deceased), besides having had blue sclerae had also had impaired hearing of the neurogenic type since the age of 37. Furthermore, out of the six children in this family one other girl, eight years old, showed markedly blue sclerae and hyperlaxibility of the finger joints. In spite of the hereditary occurrence of blue sclerae and hyperlaxibility and of one case of neurogenic deafness in this family it has not been considered justifiable to include it in the material as there is no tendency towards fractures.

I met another case showing abnormally blue sclerae but no brittle bones during the field investigation, thanks to the suggestion of a proband family. In spite of several severe injuries she had never had any fractures nor did she give other evidence of osteogenesis imperfecta. Her parents, brothers and sisters had neither blue sclerae nor any other signs of the disease. These four cases are the only ones which I have observed with blue sclerae and no demonstrable connection with brittle bones. Seedorff describes one such case.

The question as to whether blue sclerae present in families without demonstrable osseous fragility bear any genetic relation to osteogenesis imperfecta cannot at present be determined.

The criteria for the diagnosis of osteogenesis imperfecta in this material may be summarized thus:

I. For probands:
   1. Blue sclerae and idiopathic brittle bones, demonstrated by one or several fractures from inadequate trauma, *or,*
   2. Idiopathic brittle bones alone, demonstrated by at least 7 fractures not normally justified by the causative force.

II. For secondary cases:
   a) Relatives who comply with the same criteria as do the probands (1. or 2.).

b) Relatives with less severe manifestations such as blue sclerae alone or multiple fractures from inadequate trauma.

Differential diagnosis

The criteria by which osseous fragility may be described as idiopathic are that the case history, the clinical and X-ray findings and the blood chemistry do not provide any grounds for considering other causes of the tendency to fractures, such as neoplasms, infectious or inflammatory diseases, blood diseases, lipoidoses (Gaucher's disease etc.), vitamin and nutritional disturbances, endocrine dysfunction, osteitis fibrosa generalisata (v. Recklinghausen), osteitis deformans (Paget), Albers-Schönberg's and other forms of osteosclerosis, and various osteoporotic conditions.

Osteogenesis imperfecta congenita may exhibit pronounced superficial similarities to chondrodystrophy in that the skeletal parts of the extremities are greatly shortened due to multiple fractures, and thus the extremities appear short and awkward as in chondrodystrophy.

Examples of certain points regarding the differential diagnosis may be found in the report on those cases which were excluded from the basic material by reason of another or uncertain diagnosis. This report presents a survey of some of those conditions which can be confused with osteogenesis imperfecta. (See p. 28.)

V. Material and Methods

1. Material

In order to estimate the extent of osteogenesis imperfecta in Sweden, a preliminary survey was made in 1953—54 of cases of the disease which were treated in Swedish hospitals during the 10-year period 1943—1952 (Berfenstam and Smårs 1956).

In a study of the annual reports from all Swedish hospitals issued during this period (medical, surgical, pediatric, obstetric and gynaecological, orthopaedic, and ear, nose and throat departments), approximately 55 cases were found with the diagnosis "osteogenesis imperfecta" (or one of the synonyms "fragilitas ossium", "osteopsathyrosis idiopathica", "Lobstein's disease" or "Vrolik's disease"). In 20 cases the hospital records gave the information that the disease also occurred in other members of the same family, and that some 30 other certain cases were to be found. It was, however, probable that many more cases of the disease existed than those found by the preliminary survey.

The most reliable way to obtain information on cases of the disease seemed to be to inquire directly from the physician throughout the country. As the disease is rare and has such unique characteristics, it can probably as a rule be depended upon that any doctor who has met a case of it will not easily forget it.

After certain preparations were made in order to direct attention to the disease, a letter was sent in September 1956 to all the district physicians* in the country and to the heads of the hospital departments mentioned above (and in January 1957 to those of the roentgen departments)), requesting information about certain or probable cases of

* The district physicians in Sweden serve not only as public health officers but are also required to have an outpatient service. Very often they are in charge of the medical care of nursing homes and other homes for chronically ill, and homes for the aged. In some remote districts they also serve as superintendents of small hospital units.

osteogenesis imperfecta which these doctors could recall having seen. At the end of August, 1956, a few weeks before the issue of the general inquiry, an article on the disease was published in "Svenska läkartidningen" (The Journal of the Swedish Medical Association) in the form of a review and an account of the preliminary investigation made in 1953—54. At approximately the same time a similar article was published in the "Svensk sjuksköterskетidning" (The Journal of the Swedish Nurses' Association) with an appeal to nurses to report any cases observed to their nearest doctor, or direct to the author.

This inquiry to the doctors provided details of altogether 159 probable cases of osteogenesis imperfecta, including the cases about whom information was obtained in 1954.

Information was also obtained from laymen concerning 2 cases, and from earlier Swedish literature about a further case. No direct information was obtained on these 3 cases from other sources. A summary of the basic material is given in Table 1.

Of the 162 individuals about whom information was obtained, as described, it was later found as a result of investigations made after February 1957 that 15 had to be excluded for various reasons. Six of these were found not to be cases of osteogenesis imperfecta but to have other diagnoses, as: (1) probable neurofibromatosis, (2) a disturbance of unknown nature during the period immediately following birth, (3)

TABLE 1. *Basic material.*

Source of information	Total No. of cases	Cases excluded			Definite primary cases (probands)
		Diagnosis not certain	Other diagnosis	Total	
Inquiry to hospital doctors and district doctors 1956 (also including cases from the annual reports from all Swedish hospitals (1943—1952)	159	9	6	15	144
Other sources:					
Literature 1	3	—	—	—	3
Laymen 2					
Total	162	9	6	15	147

a congenital deformity of another kind, (4) osteoporosis senilis, (5) polyostotic fibrous dysplasia, (6) a slight deformity of the fingers. In the other nine cases the diagnosis was considered unreliable, either because the course of the disease was atypical or because the information available was inadequate. These cases thus excluded are discussed in greater detail in another section (page 28).

The basic material consists then of 147 certain cases which were primarily collected by this inquiry. These cases are indicated as *index cases* or *probands*. Of these it was found that 34 had died before 1957 and one had left the country. Thus, there were 112 remaining individuals whom it was possible to contact.

The index cases are distributed according to the different sources of information as follows:

Hospital doctor	General practitioner	Hosp. doctor and Gen. pract.	Hosp. doctor and Nurse	Layman	Literature
116	14	12	2	2	1

Three index cases had been reported from 5 different sources, eight from 4 sources, eleven from 3 sources, 44 from 2 sources and 81 from only one source.

Secondary cases. Among the relatives of the probands a further number of cases were discovered. Of these the information was such that it could be considered certain that they showed distinct signs of osteogenesis imperfecta. These cases are designated secondary cases.

In the case of relatives who died before the investigation took place, information was obtained partly from hospital records and partly from reliable accounts from other relatives. For those cases who were alive in 1957 and resident in Sweden, the diagnosis was always personally verified. Altogether information was obtained about 127 certain secondary cases, of whom 78 were alive in Sweden, 3 had left for the U.S.A. before 1957, and 46 had died before 1957.

A summary of the whole material is given as follows:

	Probands	Secondary cases	Total
Total material	147	127	274
of which of Swedish birth	140	126	266
» » » foreign birth	7	1	8
Emigrated to another country			
Swedish birth	—	3	3
Foreign birth	1	—	1
Died before 1943 (Swedish birth)	6	31	37
Died 1943—1956			
Swedish birth	27	14	41
Foreign birth	1	1	2
Of Swedish birth, alive 1943—1957	134	95	229
Of Swedish birth, alive and in Sweden 1957	107	78	185
Total number of cases alive in Sweden 1957 = total number of cases investigated	112	78	190

Cases of foreign birth have been shown separately as it was not considered suitable to include these cases in the genetic analysis and the frequency estimation (cf. page 28). A case of foreign birth is defined here as one whose father or mother was not born a Swedish citizen.

2. Method of investigation

a) Field investigation

Using the primary material as a basis, the field investigation was prepared in the following way during the spring of 1957. The address and date of birth of each proband case, together with date of death if deceased, and also the corresponding information on their parents, brothers and sisters and children were requested from the respective parish record offices. Of these, 152 replied, i. e. 99.3 %. To confirm the data and also to obtain a rough idea of the course of the disease and its occurrence within the family, letters were sent to those probands whose addresses had been obtained from the parish offices. Of 114 probands addressed, 87 replied, i. e. 76.3 %. Copies of the hospital records were then obtained from the various hospitals in which the patients had been treated.

Using this information the place of residence of the probands, and to a considerable extent that of their relatives, could now be mapped, and

a travel scheme planned for the field investigation. During these preparations genealogical tables had also been drawn up, and this together with the other information obtained beforehand facilitated the field investigation. This was carried out in the summer and autumn of 1957, altogether taking just over four months. The journeys were made by car, and all the counties in the country were visited. It was the original intention to limit the field investigation to only a part of Sweden, but during the course of the investigation it was found to be desirable, and also feasible, to extend it to include the whole country. Altogether a distance of 15,000 km. was covered.

As a result of the preliminary questionnaire the proband patients and a number of their relatives were acquainted with the fact that an investigation of the disease was in progress. This simplified the personal contact. When possible the visit was arranged beforehand by telephone. As many as possible of the parents, brothers and sisters and children of the probands and the secondary cases were interviewed and examined, and in certain cases even more distant relatives, particularly if any suspicion arose that they might show any signs or symptoms of the disease. Almost all appeared to be interested, and co-operated willingly. In order to investigate personally all the probands and secondary cases who were alive, and as many as possible of their relatives, it was sometimes necessary to pay more than one visit to the same place as some of the members of a family were available only at one time, some at another. A few cases which were not available earlier were investigated during a final journey in February 1958.

In this way all the probands who were alive and in Sweden and on whom information was obtained prior to the 1st January 1957, were interviewed and investigated, together with all the cases "secondary" to these who were alive and in Sweden, making a total of 112 probands and 78 secondary cases. Further, 557 relatives of the probands were investigated. Relatives of those probands who had died were also visited and investigated.

The following is a summary of the method used in collecting information about the various individuals comprising the complete material:

Personal investigation:	
Personal investigation + hospital investigation	136
Personal investigation only	54
Total	190

Other cases, not examined personally (dead or emigrated):	
Hospital investigation	37
Information from relatives alone	47
Total	84

During the field investigation one further case was reported and investigated, namely, a child with a foreign father, born in March 1957 and without any connection with the proband families. This case was not included in the material.

After the conclusion of the field investigation while the data were being studied, I was informed of four further cases, one lethal and three surviving. None of these cases are included in the material.

b) Interview and investigation

The personal interview of the patients was carried out according to a detailed scheme, prepared before the beginning of the field investigation, including questions concerning personal data, family conditions, the patient's previous and recent history of disease, and socio-medical questions — the latter with a view to making possible an assessment of the influence of the disease on the general living conditions of the patient. The investigation was carried out as a general physical examination. Details are given in the summary of the interview and investigation scheme.

The personal interviews and investigations of the healthy members of the probands' families were limited so as to obtain information on the date of birth, place of birth, present address and parish, civil state, occupation, previous and present state of health, and assessment of the colour of the sclerae, hearing test (whispering voice), examination for possible hyperlaxibility, and dental examination.

In the case of those relatives who were not available for interview, the most reliable information possible was obtained from other members of the family who were present.

c) Summary of scheme for interview and physical examination of probands and secondary cases

A. Name of the patient, date of birth, parish of birth, present address and parish, civil state, present occupation.

B. Family case history with similar information on parents, brothers and sisters and children, and information on signs of osteogenesis imperfecta in these relatives and also in more distant relatives. The parents of isolated cases were asked whether they had any illnesses before the patient's birth, or whether they had had any roentgen examinations, and whether the parents were related to one another.

C. The patient's case history:
1. Abnormal conditions before or during the birth of the patient.
2. Age at which blue sclerae were discovered, at which the first fracture occurred, at which the patient was first able to walk, at which the diagnosis was established.
3. Hospital attendances: Where? When?
4. Number of fractures and age when they occurred.
5. Lower back trouble and other spinal symptoms.
6. Hyperlaxibility and tendency to distortion.
7. The appearance of abnormal posture and deformity.
8. Age at which any impairment of hearing was first discovered. Occurrence of dizziness or singing in the ears.
9. Dental changes.
10. Skin changes.
11. Corneal changes, specifically arcus senilis.
12. Signs of increased tendency to bleeding, tendency to bruises.
13. Renal calculus or urinary calculus.
14. Other signs or symptoms with conceivable connection with osteogenesis imperfecta.
15. Periods of deterioration, exacerbating factors.
16. Treatment obtained.
17. Congenital deformities other than osteogenesis imperfecta.
18. Other diseases.
19. Intellectual capacity compared with brothers and sisters.

D. Summary of questionnaire for the socio-medical interview.
1. School: ordinary school, special school for the handicapped, other form of education. Standard reached at school, type of school, further education, e. g. university.
2. School gymnastics.
3. Military service.
4. Occupation, changes of occupation, occupational training, working conditions, other occupations.

5. Supported by own wage-earning, completely or partly. Other income. Dependent on relatives or other persons.
6. Invalid pension. Social help.
7. Age at which osteogenesis imperfecta became obvious handicap. Number of visits to doctor and journeys made for reasons of illness.
8. Extent to which (total time) osteogenesis imperfecta has prevented attendance at school or work and necessitated attendance at residential school or treatment in hospital.
9. Extent to which working ability recovered (completely, partly or not at all) after fractures or periods of deterioration. In the same work as before or other work. With or without sheltered working conditions.
10. Rehabilitation treatment: Has such been given? Of what kind? Should more rehabilitation treatment have been given? Is more rehabilitation treatment necessary?
11. Present working ability: Complete or partial ability to work or complete incapacity for working. Wage earning or work as housewife. Own employer or employed. Present income.
    Work or occupation other than wage earning. Type of work.
12. In cases of complete incapacity for work: Extent of movement and ability to care for oneself, or in need of help.
13. Contact with people in vicinity.
14. Arrangements for meals.
15. Standard of living accommodation: own accommodation or rented apartment. Modern comforts. Number of persons and rooms per apartment. Suitability of accommodation for patient's condition.
16. Throughout the whole investigation, an attempt was made to form an idea of the intellectual development and the general mental state and attitude of the patient.

E. Physical examination.
1. Assessment of general condition, body build, height, weight (information from patient), general build and muscles, any signs of cardiac decompensation, thyroid, mouth and throat, superficial lymph glands, breasts, lungs, heart, blood pressure, abdominal palpation and testing of reflexes.
2. Skeletal deformities with regard to:
   a) Form of head
   b) Thorax
   c) Back: Kyphosis, scoliosis
   d) Deformities of the extremities
   e) Flat foot
   f) Measurement of length of fractured extremity (where possible compared with the other, non-fractured extremity).
3. Signs of hyperlaxibility
4. Colour of sclerae and any other eye anomalies.
5. Dental condition.

6. Hearing (tested with whisper).
7. Skin changes.
8. General impression of intellectual development: good, moderate, not good.

3. Distribution of the material into different families. Recording and disposition of the material

The whole material, consisting of 274 cases of osteogenesis imperfecta, was distributed among 110 families, as shown in Table 2. Table 2 also lists the number of generations in which osteogenesis imperfecta has appeared in different pedigrees. The number of cases of osteogenesis imperfecta per pedigree is given in Table 3.

In 41 of these families there are two or more cases of the disease, and in 69 only one case.

The material has been classified into units, each comprising a sibship and its parents. Each sibship has been given a number, with its members

TABLE 2. *Pedigrees in which osteogenesis imperfecta occurred in one or more generations.*

No. of generations		1	2	3	4	5	6	Total
No. of pedigrees with 1—6 generations of osteogenesis imperfecta	Swedish extraction	70	18	10	4	1	1	104
	Foreign extraction	4	—	2	—	—	—	6

TABLE 3. *No of cases of osteogenesis imperfecta in different pedigrees.*

No. of cases of o. i. per pedigree		1	2	3	4	5	6	7	8	9	10	—	14	—	42	Total
No. of pedigrees	Swedish extraction	65	12	8	5	5	2	3	—	1	1	—	1	—	1	104
	Foreign extraction	4	—	1	—	1	—	—	—	—	—	—	—	—	—	6

numbered in order of birth. (See further survey of clinical data, page 216 ff.)

As mentioned previously, the aim of the study was to investigate the disease from three main viewpoints, viz.:

1. Clinical aspects.
2. Genetic and epidemiological aspects.
3. Socio-medical significance.

For the clinical study the 190 surviving cases who were alive and in Sweden in 1957 and who were examined during the field investigation, and the 22 non-surviving cases (so called osteogenesis imperfecta congenita), for which information was obtained from hospital records and from relatives, were used.

In the study of the genetic and epidemiological data those cases whose father or mother was not born as a Swedish citizen were excluded from the analysis (cf. page 22). Otherwise the complete material was used as far as was applicable for these analyses.

The study of the socio-medical significance of the disease was based exclusively on the 190 cases who were alive and in Sweden in 1957.

4. Report of a) cases excluded from the basic material and b) doubtful cases among relatives of the probands, not included as secondary cases

a) Cases excluded from the basic material

15 cases were excluded from the actual proband material due to another or uncertain diagnosis (Cf. p. 20—21.) In order to present more detailed reasons for these exclusions, some data about the cases concerned are given below:

1. A. N. Unmarried woman, 44 years old. Deformity of right lower leg from birth. No fractures later. No familial history of osteogenesis imperfecta. Pseudarthrosis right lower leg. Sclerae normal. Hearing good. Finger joints somewhat hyperextensible. Pea-sized and larger fibroma-like tumours over the whole body. Conclusion: Disease picture points primarily to multiple neurofibromatosis which can also explain the deformity.

2. K. H. Man, 40 years old, reported on account of multiple fractures from the age of 2 years, and pronounced deformities. Study of the hospital records and information from the doctor who treated him reveal that the diagnosis is that of polyostotic fibrous dysplasia (Albright's syndrome), characterized by osseous fragility caused by hypostotic and denser hyperostotic centres.

3. I. G. Woman, 83 years old, reported on account of three fractures (obviously with adequate cause) at the ages of 52, 73 and 81 years, and osteoporosis with vertebral compressions revealed at the age of 74 years. No familial history. Sclerae not blue. Hearing good. The osteoporosis may be explained by her age, and confinement to bed after femoral neck fracture. Conclusion: Probably senile osteoporosis.

4. G. O. Boy, 1 1/2 years old, reported by reason of congenital malformation and slight blue tinting of the sclerae. Examination six months later showed: Sclerae not definitely abnormally blue. No fractures but congenital luxation of the hip joint, atrophy of the subcutaneous fat, mentally very backward.
Conclusion: Congenital malformation, but no grounds for diagnosing osteogenesis imperfecta.

5. R. P. Girl, 3 years old, reported because of roentgenological signs of an ossification disturbance with decalcification at the age of 2 weeks. Normal roentgen picture at the age of 6 weeks. Examination at 3 years old revealed that she had never had fractures. No blue sclerae. No other signs of disease. No familial history.
Conclusion: No grounds for diagnosing osteogenesis imperfecta.

6. G. Y. Man, 29 years old, reported on account of malformation of right thumb, slight hyperextensibility of finger and toe joints, and doubtful blue tinting of the sclerae. Had never had a fracture. Examination: Blue shading of sclerae but within the normal variations. Family investigation negative.
Conclusion: No grounds for diagnosing osteogenesis imperfecta.

7. M. O. Woman, 35 years old. At the age of 12—14 months (1923) was treated in hospital and diagnosed as osteogenesis imperfecta with rickets. At that time a large fontanelle, craniotabes, rachitic rosary and several fractures of the arms and legs were found. The sclerae were not mentioned. After antirachitic treatment she was discharged as improved. According to recent information from the mother and two sisters (the patient herself refuses to be visited), she has been physically well and has had no fractures since the age of 1 year. The mother and sisters mentioned spontaneously that the patient was boarded out as an infant, and at that time received extremely deficient nourishment, "mostly sugared water". Both the hospital records and the information from the relatives provide evidence that the whole disease picture might be explained by a severe nutritional deficiency. The subsequent history is contradictory of a diagnosis of osteogenesis imperfecta.
Conclusion: Diagnosis of osteogenesis imperfecta uncertain.

8. M. H. Boy, 9 years old, suspected of having osteogenesis imperfecta because of 5 fractures, caused by moderate injury between the ages of 4 and 8 years. Examination: No blue sclerae or other signs of osteogenesis imperfecta. No familial history.
Conclusion: Insufficient grounds for diagnosing osteogenesis imperfecta.

9. H. L. Woman, born 1860, died 1939. Treated in hospital 1939 with diagnosis of acute bronchitis with cardiosclerosis and idiopathic osteopsathyrosis. The latter diagnosis appears to have been made by reason of the following: Two femoral neck fractures at the ages of 60 and 70 years respectively, and one fracture of the lower arm at the age of 73 years, a certain degree of hyperextensibility in the finger joints, and added to these the fact that a daughter had had one fracture and a sister several fractures. Blue sclerae were apparently not to be found in the family.
Conclusion: Insufficient grounds for diagnosing osteogenesis imperfecta.

10. E. A. Woman, 69 years old. Her lower leg was first noticed to be bent at the age of 1—2 years. A correction operation at the age of 30 years was unsuccessful. There had been a certain amount of difficulty in walking ever since childhood, but she had worked and looked after the home up to the age of 43 years. Subsequently she was unwell with hypertonia, diabetes mellitus and severe headaches. Her first fracture was at 59 years old, after a fall off an invalid cycle which she had just begun to use. She was treated in hospital at the age of 66 years for a lower arm fracture caused by very slight injury, and at the age of 69 years she had a lower leg fracture for an unknown reason. Examination: Sclerae — normal colour. Moderate degree of kyphoscoliosis. The extremities appear to be rather short in relation to the body. Pronounced dorsal convex curvature of lower arms, lateral convex curvature of femurs and forward convex curvature of lower legs. Family: Out of three brothers and two sisters, two brothers have had deformities of the extremities similar to those of the proband since childhood. One of these was examined, and showed changes similar to those of the proband, with also a pronounced kyphotic curvature of the whole back. His sclerae were normal. The parents are said to have been well. The hospital diagnosis for both the proband and her two affected brothers was originally chondrodystrophy, but after the fracture at 59 years the proband was diagnosed as osteopsathyrosis. Discussion: The two pathological fractures at 66 and 69 years respectively might be due to either osteogenesis imperfecta, senile osteoporosis or the osteoporosis of inactivity. The deformities may be due to osteogenesis imperfecta, but it is also conceivable that they may be due to some non-typical chondrodystrophic condition. Conclusion: Diagnosis of osteogenesis imperfecta uncertain.

11. I. N. Woman, 43 years, with bilateral congenital luxation of the hip joint. Otherwise well until a pregnancy at the age of 28 years, when she had a Caesarian section because of a narrow pelvis. Subsequently she had pains in the back and legs and difficulty in walking. X-ray examination showed osteoporosis with "fish vertebrae and vertebral compressions". Serum calcium and

phosphorus values were normal. Sclerae: slight blue shading but within normal variations. Hearing normal. She has had only one fracture, an effect of an adequate cause. No familial history.
Conclusion: The case may be an example of osteoporosis arising after pregnancy (cf. Nordin and Roper, 1955), and the diagnosis of osteogenesis imperfecta is probably not justifiable.

12. L. H. Girl, 3 1/2 years. Immediately after birth it was observed that the skull was unusually soft. Roentgen examination showed ossification disturbances with wide fontanelles and sutures and a large number of non-fused bone islets. The interpretation was osteogenesis imperfecta. No other skeletal changes were observed either at that time or later. No fractures. Sclerae abnormally blue. Some degree of hyperlaxibility in finger joints. Pes plano valgus. No familial history.
Conclusion: The case could probably be interpreted as an abortive form of osteogenesis imperfecta, but as it did not show the diagnostic criteria, it was not sufficiently definite to be included in the material.

13. K. Z. J. Boy, 7 years old. Immediately after birth roentgen examination showed bilateral curvature of femur, tibia and humerus, but no signs of fractures. At the ages of 2, 5 and 6 years, fractures caused by moderate trauma. Normal white sclerae.
Conclusion: This case could also be interpreted as a probable abortive form of osteogenesis imperfecta, but it was regarded as too uncertain to be included in the material.

14. M. M. Girl, 17 years old. Blue sclerae and hyperlaxibility. No fractures. Her father and a sister also had blue sclerae but no fractures, and the father also had impaired hearing of the neurogenic type from the age of 37 years. The family is discussed in the section "Diagnostic criteria".
Conclusion: The case did not comply with the diagnostic criteria and was not included in the material.

15. S. L. Boy, died at the age of 2 months. Diagnosis: Congenital softening of the skull (osteogenesis imperfecta). No information as regards fractures or colour of sclerae.
Conclusion: As there was insufficient information to support the diagnosis, the case was not included.

b) Doubtful cases among relatives not included as secondary cases

During the family investigations 15 individuals were encountered regarding whom some degree of doubt arose as to whether or not the signs of osteogenesis

imperfecta could be considered to exist. They have therefore not been included in the material, but it is deemed justifiable to give a short account of these cases.

Seven of the cases died before 1957, and the only reliable information could be obtained from relatives. The other eight were alive and were investigated.

1. F. E. Man, 44 years old. Maternal uncle to proband 34:1 (cf. pp. 129—130), who had blue sclerae and osseous fragility. Sclerae possibly but not certainly abnormally blue. No fractures or other signs of osteogenesis imperfecta.

2. M. S. Girl, 11 years old. Cousin of proband 34:1p (see above) and daughter of secondary case 33:7, who has obviously blue sclerae but no fractures. Sclerae: possibly but not certainly abnormally blue. No fractures or other signs of osteogenesis imperfecta.

3. P. J. Boy, 7 years old. Brother of case No 34:1p (see above). Sclerae possibly but not certainly abnormally blue. No fractures or other signs of osteogenesis imperfecta.

4. K. K. Boy, 14 years old. Son of case No. 35:Fp and brother of No. 35:2p (cf. p. 16), who both have idiopathic fragility but no blue sclerae. Has had two fractures at the ages of 11 and 14 years respectively, after moderate trauma, one caused by a fall on ice, and the other when he jumped and fell. Otherwise no signs of osteogenensis imperfecta.

5. L. P. Woman, born 1863, died 1952. Mother of case No. 42:M and maternal grandmother of No. 42:1 and No. 43:F, all of whom had fractures and blue sclerae. One fracture at 14 years and two fractures after the age of 60 years. According to information by a son, did not have blue sclerae.

6. U. N. Girl, 13 years old. Sister of case No. 46:1 and daughter of 46:M, both of whom had blue sclerae and tendency to fractures. Possibly but not certainly abnormally blue sclerae. No fractures or other signs of osteogenesis imperfecta.

7. B. N. Woman, born 1884, died 1929. Mother of case No. 50:M and maternal grandmother of No. 50:2p, both with tendency to fractures, and blue sclerae. No fracture so far as is known. Contradictory information as regards blue sclerae.

8. A. J. Woman, born 1876, died 1947. Mother of case No. 53:Mp and maternal grandmother of No. 53:1, both of whom had blue sclerae and tendency to fractures. Contradictory information as regards blue sclerae. Somewhat hyperextensible joints. No fractures. Hearing was good.

9. I. Å. Woman, 39 years. Sister of No. 53:Mp and maternal aunt of No. 53:1, both with blue sclerae and tendency to fractures. Had had one fracture of moderate cause. Possibly but not certainly abnormally blue sclerae. Finger joints somewhat hyperextensible.

10. N. E. G. Boy, born 1936, died 1939. Son of case No. 51:3p, who has blue sclerae and tendency to fractures. No fractures. Contradictory information as regards colour of sclerae.

11. U. R. Girl, born 26/2 1936, died 22/3 1936. Daughter of case No. 80:M, who has blue sclerae but no fractures, and sister of No. 80:2, who has both blue sclerae and tendency to fractures. No fractures. Blue sclerae, according to the mother. This information should however be taken with reservation, as the child died at the age of three weeks.

12. A. E. Woman, born about 1878, died about 1905. Great-aunt of case No. 145:2p, who has bone fragility and blue sclerae. Uncertain information as regards blue sclerae. No fractures so far as is known.

13. H. O. Man, born 1883, died 1942. Maternal grandfather of No. 145:2p, who has bone fragility and blue sclerae. No fractures. Somewhat impaired hearing from the age of 30—40 years. Uncertain information as to colour of sclerae.

14. G. A. Woman, 48 years. Maternal aunt of case No. 145:2p (see above). Two fractures of moderate cause. Sclerae show blue shading but within normal variations.

15. M. L. Girl, 11 years old. Sister of No. 145:2p (see above). No fractures. Possibly but not certainly abnormally blue sclerae. Somewhat hyperextensible finger joints.

All these cases have thus been considered as uncertain and were not included in the material.

5. Degree of completeness and representativeness of the material

A critical review

a) Degree of adequacy of the method used for collecting the material

Various methods are used in statistical and genetical studies of different diseases. In principal there are two main methods. One is the random method, in which probands are selected by random collection through a whole population, and thus all individuals have a similar chance of being selected; the occurrence of the disease is then also studied among the relatives of the probands. This method is, of course, unsuitable for

the investigation of such an uncommon disease as osteogenesis imperfecta. In the other main method the whole population within a limited geographical area is investigated; an attempt is then made to trace individuals with the disease in question, recorded either at a certain definite time or over a relatively long period.

If only those cases registered at a certain definite time are included, it must be presupposed that only a small part of the available material will be found. If, on the other hand, the recording extends over a longer period the chances of obtaining a more complete material are considerably increased.

The principle used in collecting this material follows most closely the latter method, called by Sjögren (1954) the p e r i o d m e t h o d. *Attempts have been made to trace all cases of the disease who were alive and in Sweden during the period 1943—1955* (a period of 13 years).

The geographical area chosen was that of the whole of Sweden, partly because of the wish to get some idea of the extent of the disease in the country, and partly because of its rarity. The aim was to collect, despite the rarity of the disease, a material as large and as representative as possible.

In dealing with a disease which is principally manifested in a certain age period, there is a risk, if a cross section survey is taken during a certain limited period, of missing those cases in whom the disease was evident only in the past. This risk must be taken into consideration, especially when the survey period is as short as 13 years.

As mentioned above, the collection of the material was made from two different starting points, firstly, by going through the annual reports containing the diagnosis registers of the Swedish hospitals for the years 1943—1952, and, secondly, by means of a questionnaire sent to doctors. In the first-named method the period was strictly limited to ten years. In the questionnaire, on the other hand, information was requested about all individuals with osteogenesis imperfecta that they could recall ever having observed. There is good reason to suppose that any doctor who has seen and treated a case of osteogenesis imperfecta will not easily forget it, owing to its rarity and to a great extent unique characteristics. This was found, at least to a certain degree, to be the fact, as cases observed as far back as around 1920 were reported.

Attempting in this way to gain information covering a longer period of time than the actual survey period I also hoped to find otherwise

untraced cases belonging to the investigation period, i. e. through parents or other relatives who had been previously treated for the disease.

Even if the investigation, as applied to the frequency of the disease, was limited to cases who were alive during the 13 year period 1943—1955, the collection of material thus covered a longer, undefined period.

There was also a greater possibility that every case of the disease would be reported, as very often more than one doctor had treated a particular patient, and it is therefore probable that the reports overlapped one another to a certain degree. As mentioned on page 21, 66 of the 147 primary cases were reported from two or more sources.

Of 867 district physicians and 299 hospital chief physicians to whom letters were sent (total 1166), 823, i. e. 70.6 % replied, a fairly satisfactory reply-rate.

Of those cases which were traced by means of the preliminary study of the annual reports for the years 1943—1952, all were reported in the 1956 inquiry, which would seem to support the adequacy of the inquiry method.

Another proof that the collection of material was relatively complete is the fact that no new information about further cases outside the proband families was obtained either through any of the probands, secondary cases or their relatives. As is often the case in certain diseases, they had a fair amount of knowledge of one another, but no new case was traced in this way. By this means, however, one reported proband was found for whom the wrong address had previously been given.

The circumstances mentioned above suggest that through the questionnaire *the majority of the cases in the country of whom the doctors had any knowledge were contacted.*

On the other hand, it may be presupposed that those cases with the disease who did not need to visit a doctor or a hospital for fractures or deformities during this period, or, whose fractures appeared to have a natural explanation and therefore did not attract any special attention, could have escaped diagnosis and report. As will be seen below, the secondary cases are to a great extent individuals in whom the disease manifestations were less striking, but who were discovered through relatives who have the disease in a more severe form.

An example of individuals who might not have been reported, are persons now about 40—70 years old, who 20—50 or more years ago were under 20 years of age and then had their periods of osseous fragility,

but who later became stabilized and no longer in need of treatment. Since most of these cases were treated by doctors who have now retired from practice, it is unlikely that they would be discovered; if it so happened that they had younger relatives or children with the disease in a manifest form, they could however have been included as secondary cases, but otherwise the chance is that they would be missed.

As mentioned in the discussion on the diagnostic criteria, a group of cases with bone fragility alone and lacking blue sclerae have been included in the material. To what degree a number of the doctors to whom the inquiry was sent believed that such cases should not be counted as osteogenesis imperfecta, and therefore did not report cases of this type, is not known. The questionnaire demanded information relating to certain or probable cases of osteogenesis imperfecta. The collection of the material by means of the questionnaire rests, of course, on the diagnosis of osteogenesis imperfecta by the doctors in question, and their conception of this disease.

b) Degree of completeness of the material assessed by that part composed of secondary cases

In order to assess the degree of completeness of the material it is of value to study the secondary cases. The 95 secondary cases who were alive during the period 1943—1955 can to a certain extent be considered as representative of cases of osteogenesis imperfecta who were not discovered through the questionnaire or through the hospital annual reports. They were collected solely through their relationship to the proband families.

It is convenient for this analysis to divide the secondary cases into three groups: 1) those who have at some time been diagnosed by a doctor as osteogenesis imperfecta, 2) those who have never been diagnosed as osteogenesis imperfecta in spite of previous treatment for fractures, or, in some cases, for back troubles, and 3) those who have never been diagnosed and, as far as is known, have never undergone treatment by a doctor or in a hospital for the disease.

Group 1 a) Cases diagnosed and treated in a hospital during the period 1943—1955: 7 cases. Of these cases one had had altogether 30 fractures and had typical deformities, and had been the subject of repeated clinical demonstrations as a patient up to 1943. It was therefore surprising that it had not been reported as a result of the inquiry. Another case also had pronounced deformities, but the hospital treatment had ended before 1937, after which only one consultation at the out-patient department in 1945 is noted. It was more understandable therefore that this case was not remembered. The remaining diagnosed cases had had 1—7 fractures and did not have any striking deformities. It must be noted, however, that all seven cases should have been included in the inquiry result, as they had been diagnosed. The fact that this was not so points to a certain degree of incompleteness.

Group 1 b) Cases diagnosed and treated in hospital or by doctors only before but not after 1943: 3 cases. One of these, who had had about 12 fractures, was diagnosed in 1919, another, who had had 5 fractures, in 1935, and the third, who had had 8 fractures, in 1934. All three cases had thus been diagnosed and treated more than 20 years before the inquiry. The two first-named cases had not been disabled and were quite fit for work, and, in addition, the doctor who made the diagnosis for one of the cases in 1935 had died. The third case was an invalid man who lived an isolated life and had not visited a doctor since 1934.

Group 2 a) Cases not diagnosed in spite of hospital care during the period 1943—1955: 20 cases. This group includes one case with blue sclerae and no fractures, who was treated in hospital for a prolapsed disc, nine cases with blue sclerae and 1—2 fractures, nine cases with 3—8 fractures, seven of whom had blue, and two normal white sclerae, and one case with blue sclerae and more than 10 fractures, which, however, usually occurred with an adequate cause. Apart from one 70-year old man with pronounced kyphosis, there were no pronounced deformities. However, as all the cases except two had blue sclerae, a careful examination could have made the diagnosis possible in at least some of the cases. For one of the cases with two fractures the examining doctor at the hospital had noted blue sclerae, but this had not been mentioned in the final diagnosis. It is perhaps not surprising that blue sclerae have passed unnoticed in the other cases. When a patient is admitted to hospital for a fracture with no special peculiarities either in its occurrence or in its nature, it is natural that the doctor directs his attention on the fracture alone and may overlook a minor symptom such as blue sclerae. Hardly any of the twenty cases in group 2 a) had symptoms so obvious as to arouse special attention.

Group 2 b) Cases not diagnosed in spite of medical treatment (not in hospital) in the period 1943—1955: 21 cases. Of these cases all except one had blue sclerae, fourteen had had 1—4 fractures, five 5—8 fractures and two 10—12 fractures. None of the cases had any pronounced deformities.

Group 2 c) Cases not diagnosed although examined by a doctor or in hospital before 1943 (the majority more than 20 years before the inquiry): 23 cases. Of these cases all except two had blue sclerae, seventeen had had 1—4

fractures but no pronounced deformities, and one had more than 10 fractures but no deformities at all. In one further case, a woman born in 1918 and who died in 1953, it was reported that she was fully mobile in early childhood but that during her school years she had several fractures (5—10) and developed deformities until she was finally completely disabled and could do nothing but sit in a chair. She was last treated for a fracture in hospital in 1933, and no diagnosis other than that of this fracture is mentioned in the hospital record. After 1933 she visited various doctors for advice, but as it seemed that there was nothing to be done, both she and her parents soon abandoned further visits.

In all the cases in group 2 some requirements for forming a diagnosis were to be found, as they had been under medical care for fractures or other symptoms of the disease, but as, nevertheless, osteogenesis imperfecta was not diagnosed, the cases could not be reported.

Group 3 a) Cases not diagnosed and never medically examined: 10 cases. Of these cases eight had never had any fractures but did have blue sclerae, and two had blue sclerae and had had one fracture.

Group 3 b) Cases who had not been diagnosed but about whom their relations could state with certainty that they had had fractures and blue sclerae, but did not know whether they had had hospital or other medical treatment: 11 cases. Eight of these cases were born in the years 1867—1893 and died 1943—1956. The majority were said to have had the fractures in their youth, and none were said to have been disabled. The remaining three cases had emigrated to the U.S.A. many years previously and no information regarding their medical care was available.

In the study of the 95 secondary cases who were not reported as a result of the inquiry, the following is thus of relevance:

1. Seven of the 95 secondary cases were diagnosed after 1942 and should have been reported primarily through the inquiry, for this to be considered complete. A further three cases had been diagnosed before 1943 (actually before 1936, i. e. over 20 years before the inquiry), and there should also have been some possibility of tracing them through the inquiry.

2. In a further 64 cases certain requirements for forming a diagnosis were found, as they had undergone hospital or other medical care for signs (as a rule fractures) of the disease. The signs of osteogenesis imperfecta were not striking, however, in any of these cases, and this was evidently the reason that it was not diagnosed and that the cases were therefore not reported through the inquiry.

3. Of the remaining 21 cases the majority seem to have been of such a mild type as to need little treatment, and the requirements for forming a diagnosis were not found. Added to this is the fact that in some cases

the fractures occurred so long ago that in spite of any medical care given and diagnoses made they could hardly be expected to be included in the inquiry.

Without a closer study of the large number of secondary cases there could be reason to doubt the reliability of the inquiry method — ratio of probands: total number of cases found alive 1943—1957 (in the purely Swedish material, see page 22) = 134: 229 = 0.59 —. It is however evident from an analysis of the 95 secondary cases that only seven (possibly 10) of these could be expected to be reported. It could be assumed that the inquiry would only trace diagnosed cases of the disease, and mainly those who had been observed during the last 20 years (especially after 1943). Thus if only those cases who were diagnosed after 1943 are counted, the ratio Reported probands: Expected probands, is

134: (134 + 7) = 134: 141 = 0.96.

If those cases who were diagnosed with certainty even before 1943 are included, the quotient mentioned = 134: 144 = 0.93.

This strengthens the supposition that *the great majority of the diagnosed cases of the disease for the period in question were collected by means of the inquiry.*

To summarize, the following points may be made, supported by the above discussion and the study of the secondary cases:

1. There seem to be grounds for believing that the reports are almost complete (over 95 %) for those individuals in whom the symptoms were so striking during the period 1943—1955 that the diagnosis was made during this time.

2. It is conceivable that a number of those cases, now between the ages of about 40 and 70 years, who 20—50 or more years ago were under 20 years of age, having then most of their fractures and later becoming stable and not being in need of treatment, have been missed in the reports if they did not belong to the same families as the cases mentioned in point 1.

3. Another category which may not have been included in the material consists of those individuals for whom the symptoms were too mild both in themselves and in their relatives for the disease to be diagnosed and reported.

c) Degree of completeness of the material, assessed by its distribution into age and sex

The age and sex distribution in those cases in the material who were alive in Sweden in 1957 may be seen in Table 4, which also gives, for comparison, the age and sex distribution within the whole population in Sweden for the same year.

It may be seen that the material collected deviates from the whole population in the following respects:

Both sexes above 40 years of age are underrepresented and also to a lesser degree those under 10 years, while there is a marked overrepresentation of men in the ages 10—39 years, which is statistically highly significant ($P<0.001$) for males 10—19 years old. These relationships are shown in Table 5, where the frequency of osteogenesis imperfecta per 100,000 in the general Swedish population is given. In assessing the significance of frequency values in the different age groups, random variations due to the small numbers should, however, be taken into consideration.

TABLE 4. *Distribution according to age and sex of affected individuals living in Sweden 1957 and of mean population 1957.*

Age group (years)	Individuals with osteogenesis imperfecta						Mean population 1957 in Sweden		
	No. of individuals			in per cent			in per cent		
	Males	Females	M+F	Males	Females	M+F	Males	Females	M+F
0— 9	11	13	24	10.4	15.5	12.6	15.5	14.6	15.1
10—19	30	14	44	28.3	16.7	23.2	15.4	14.7	15.0
20—29	17	12	29	16.0	14.3	15.3	12.2	12.0	12.1
30—39	17	14	31	16.0	16.7	16.3	14.6	14.3	14.4
40—49	11	14	25	10.4	16.7	13.2	14.7	14.4	14.6
50—59	10	9	19	9.4	10.7	10.0	12.3	12.7	12.5
60—69	6	8	14	5.7	9.5	7.4	8.7	9.6	9.1
≧70	4	—	4	3.8	—	2.1	6.5	7.7	7.1
Total	106	84	190	100	100	100	100	100	100

TABLE 5. *Number and frequency in the general Swedish population of affected individuals living 1957. Distribution according to age and sex.*

Age group (years)	General population			Individuals with osteogenesis imperfecta					
				Number			Frequency per 100 000		
	Males	Females	Both sexes	Males	Females	M+F	Males	Females	M+F
0— 9	570,954	539,723	1,110,677	11	13	24	1.93	2.41	2.16
10—19	565,882	542,553	1,108,435	30	14	44	5.30	2.58	3.97
20—29	449,298	443,977	893,275	17	12	29	3.78	2.70	3.25
30—39	536,647	527,061	1,063,708	17	14	31	3.17	2.66	2.91
40—49	540,985	532,287	1,073,272	11	14	25	2.03	2.63	2.33
50—59	453,810	468,975	922,785	10	9	19	2.20	1.92	2.06
60—69	318,192	353,899	672,091	6	8	14	1.89	2.26	2.08
≧70	238,857	283,897	522,754	4	—	4	1.67	—	0.77
Total	3,674,625	3,692,372	7,366,997	106	84	190	2.88	2.27	2.58

The frequencies for both sexes combined decrease relatively evenly after the age period 10—19 years. An investigation of the mortality rate, using as a basis the ages reached by cases in the material who died, has, however, given no support to the suggestion that the death rate may be higher for the osteogenesis imperfecta material in its entirety than for the rest of the population. A hypothesis that a relative overrepresentation of severe cases might occur in the lower age groups, which could mean a higher disappearance rate, i. e. increased mortality rate, for such cases, could not be confirmed in the material investigated. The degree of physical handicap shows no marked connection with age, either in men or women. A somewhat constant frequency of the disease in the different age groups should therefore be expected.

Various explanations can be given for the degree of deviation from the expected frequency, found in the material. As has been pointed out previously, there is reason to suppose that a greater number of persons over 40 years of age may have been overlooked than those of younger age groups. In this respect there can be a certain degree of incompleteness in the material. This should explain why the frequencies observed are lower than those expected in these age groups.

The actual low frequency of cases in the youngest age group (0—9 years) may partly be explained by a low marriage frequency in the age group 20—29 years in this material, and a small number of children born in marriages of less than 10 years' duration (see pp. 191—193 and Tables 51 and 52 in the socio-medical section). This deviation from the frequency in the general population thus seems to a great extent to be a true one. The deviation may also be partly explained, to a lesser extent, by the fact that a small number of the patients do not sustain fractures until after the age of ten years, and hence are not diagnosed before that age.

It may seem somewhat strange that men show a higher frequency than women between the ages 10 and 39 years, and that this is especially marked for youths between 10 and 19 years of age. If random variation is disregarded, the most reasonable explanation would seem to be that the recording of female cases, including those of ages 10—39 years was incomplete. There has been no reason to suppose that there is any real frequency difference between the sexes (see page 134). The fact that a more complete report was made for men, especially at these ages, is probably due to the differences in milieu and working conditions between the two sexes. Both at work and play, men are more liable to the risk of fractures. They therefore have a greater chance of being diagnosed and recorded, particularly since medical care and treatment have been so much improved and extended during the last few decades. As the families in general are relatively small, it follows that women have been recorded to a lesser extent than men.

It appears probable from the above that the very great majority of male individuals with osteogenesis imperfecta, of ages 10—39 years, were receiving treatment and were diagnosed during the period 1943—1955. It is also probable that almost all the male patients in these age groups were reported, and that the figure obtained for them corresponds to the true one. It would therefore seem justifiable to use these figure as a basis for a frequency estimation.

d) The representativeness of the material

Both for the clinical assessment of osteogenesis imperfecta with the help of this material, and for the genetic analysis, it is desirable to know how representative it is. It is apparent from the above that the material cannot be regarded as complete. As will be discussed later (cf. page 46), it is probable that in 1957 there were about 300 patients with osteogenesis imperfecta in Sweden. Of these, 190 were recorded, i. e. just over 60 %. It would have been desirable, of course, to reach a higher figure. More effective methods than those used here for collecting the material, were, however, not practicable. The question is whether those individuals who were not recorded could prejudice the representativeness of the material.

As regards the representativeness of the material *from a clinical aspect,* the following points seem relevant. As was shown in the foregoing pages two main categories of cases could possibly have eluded the survey. The first category includes persons over about 40 years of age, whose active disease period and diagnosis was too far back for them to be reported in the inquiry. The other category consists of persons for whom the symptoms were too mild both in themselves and in their relatives for the disease to be diagnosed and reported. This category seems to include more females than males.

As regards the category of persons over 40 years of age, there are no reasonable grounds for suspecting that they were especially severely affected by the disease, or otherwise misadapted. Had they been so, there would have been a relatively greater chance of their being known to the district doctors and district nurses. This would also apply if they had been permanently cared for in nursing homes or other homes for the chronic sick. (Cf. footnote p. 19)

It is more probable, that in these unknown patients over the age of 40 years the liability to fractures was reduced after the age of 15—20 years, and therefore they have not needed to visit a doctor during the last 20—50 years and have been able to live a relatively normal life. It is of course impossible to assess the proportions to which different degrees of severity of the disease occur in this unknown group. There is no reason, however, for supposing that these unknown patients would constitute a selection as regards degree of severity or social adaptation. It may, therefore, be assumed that this group has its full counterpart in the recorded material.

The absence of the second category, unknown mild cases, may conceivably influence the clinical representativeness of the material in such a way that severe cases show a higher frequency than that which is actually true. It is difficult to determine the degree of underrepresentation of slight cases, and to what extent it has any significance in the clinical assessment of the disease. This is probably not reduced to any great extent.

A third, small group of unrecognized patients are those under about 10 years of age, who at the time of the investigation had not yet had any fractures. This group is probably of less significance.

It may seem that 60 % of the total number of individuals affected is somewhat too small to use as a basis for an assessment of the disease. In consideration of what has been discussed above, regarding those cases who may be assumed to have missed being recorded, it seems probable that it is primarily the mild cases who are somewhat underrepresented. The material may nevertheless be regarded as well suited as a basis for both a clinical and a socio-medical assessment of the disease.

Regarding *the genetic analysis* of an incomplete material, there is a greater probability of collecting families in which cases of the disease are already known. In other words, there is a risk of losing a number of those families which only have one affected child. It is, of course, of importance for the genetic analysis that the familial material should not have any bias in this respect. In a disease with simple dominant heredity, the risk of selection would seem to be smaller, however, as in most cases the disease is established in one of the parents. It is, nevertheless, of interest to investigate whether families with *one* affected child are underrepresented in the present material. This may be done by comparing the observed with the expected number of families of this type.

A comparison gives the following results*:

Family size (No. of children)	No. of families	Families with only one affected child	
		Observed No.	Expected No.
2	20	8	13.3
3	12	6	5.1
4	12	2	3.2
≥ 5	20	1	1.7
Total	64	17	23.3

From the composition of the material, it would be expected, as regards family size, that only *one* affected child would be found in 23 out of 64 families. In actual fact 17 families were observed with only one affected child, a deviation which is not significant ($P>0.05$).

From this it would seem justifiable to assume that the material does not show any bias towards the families with several cases, and that in this respect it may be regarded as representative, and used as a basis for a statistico-genetic analysis of the disease.

* The probability of a family having only one affected child is $\frac{spq^{s-1}}{1-q^s}$ and the expected number of such families is $n \frac{spq^{s-1}}{1-q^s}$, where n is the observed number of families of size s (children), and p $(=1-q)$ the probability that one child is affected. Under the assumption of dominant heredity (see section IX), $p=q=0.5$. Only families with at least two children are, of course, eligible for the investigation.

VI. An estimation of the frequency of osteogenesis imperfecta

If it is accepted that in males between the ages of 10 and 39 years the registrations were complete (cf. page 42), and their frequency is used to calculate the total number of cases of osteogenesis imperfecta in the country, a figure of 304 cases for the year 1957 is obtained. This corresponds to a frequency of 4.1 per 100,000 of the whole population. It is assumed here that the frequency for men and women is similar, an assumption for which, as mentioned above, there are good grounds.

If on the other hand the observed frequency in males between the ages of 10 and 19 years is used as the basis, a total of 390 cases (5.30 per 100,000) is obtained for the same time period. It would hardly seem justifiable, however, to consider this high figure as a true one. An extreme figure may have been obtained due to random variation. The possibility cannot be precluded, however, that there is a certain overmortality rate for the more severe cases in the older age groups, even if this could not be established from the material itself.

If, as a third alternative, the figures obtained from the secondary cases are used as a basis for the calculation, i. e. that approximately 95 % of all cases diagnosed were reported (cf. page 39), a total figure of 200 is obtained, which must be regarded as an absolutely minimal figure.

To summarize, it may be said that in estimating the total number of cases of osteogenesis imperfecta in Sweden in 1957 a minimal number of 200 and a maximal number of 390 are obtained, and that the most probable figure seems to lie almost half way between the two, i. e. approximately 300 (304 — see above), which should correspond to a frequency of 4 cases per 100,000 of the total population.

VII. Clinical aspects of osteogenesis imperfecta

In the extensive literature which has grown up around osteogenesis imperfecta, all the symptoms of the disease known up to the present time have been described in detail. As mentioned in the introduction, there have, however, been few systematic investigations on the different manifestations of the disease in any large number of cases. Seedorff (1949) alone has studied a larger, more systematically collected material, of which it appears he personally examined about 60 cases (cf. p. 6).

A study of the clinical picture based on a uniformly carried out investigation of 190 systematically collected surviving cases of the disease, together with an account of 22 lethal cases, information of whom was obtained from hospital records, would therefore seem to be justified as a complement to earlier descriptions. From a clinical aspect the material can in general be regarded as well suited for an assessment of the disease, as discussed previously (see p. 43).

In a disease such as osteogenesis imperfecta, which often leads to more or less pronounced disability, it is of great value from the point of view of description to obtain some information on how the disease in its different manifestations has affected the adaptation to community life. In order to obtain a more complete picture of the disease, it is therefore desirable to consider the socio-medical as well as the purely clinical aspects. This, as mentioned previously, was made the subject of a special study (see p. 172 ff.).

An account is first made in the following of the classification of the different degrees of severity, which has been used in the description of the material. After a survey of the symptoms included in the disease picture, these are then described and analysed separately. Finally a summarizing description is made of the usual course of the disease, and the possibilities found for influencing it.

A. Different degrees of severity of the disease

As discussed in the chapter on terminology, it is probably most correct to assume, as did Looser (1906), that there is only *one* form of the disease, which appears in different degrees of severity, between which it is not possible to draw any distinct boundaries.

From a practical point of view it is however convenient to differentiate between

1. Non-surviving (lethal and sublethal) cases, named by Looser "osteogenesis imperfecta congenita", and
2. Surviving cases, named by Looser "osteogenesis imperfecta tarda".

There would seem to be no justification in dividing the "lethal" cases into different degrees of severity, even if large variations are found, ranging from intrauterine death to survival for several months after birth.

For both the clinical and the socio-medical analysis of the surviving cases, it is convenient to divide them according to the degree of impediment of movement. The 190 surviving (so called "tardive") cases were thus classified:

1. No physical handicap (no difficulty in movement).
2. Slight physical handicap (slight difficulty in movement).
3. Fairly severe physical handicap (much difficulty in movement, but not in need of an invalid chair).
4. Severe physical handicap (invalid chair required).

In assessing the degree of movement handicap for this classification, consideration was paid mainly to the ability to move about but also to a lesser extent to the capacity for using the other extremities, with particular attention to manual dexterity.

Seedorff (1949) attempted to divide the so-called tardive cases he described into two degrees of severity, according to whether fractures occurred around the neonatal period (severe cases, type II), or whether they did not occur until after the age of approximately 2 years (mild cases, type III). He stated, as a general rule, that the earlier the first fracture or manifestation occurs the more disabling the disease becomes. It appears, however, that his classification on the basis of the above types was not completely successful, as he seems also to have been

obliged to take into consideration anatomical defects and deformities, and possibly also the degree of functional impairment.

In the study of the present material, different systems for a classification according to the degree of severity have been tested. It proved almost impossible to use the age of occurrence of the first fracture or other manifestation as a basis, as there were several individuals who had fractures already at birth with subsequent relatively slight disability. Others, on the other hand, in whom neither fractures nor deformities were observed at birth or during the first year of life, later had a greater number of fractures and developed disabling deformities. It should be pointed out, however, that the course of the disease in certain cases is so severe even from birth, that it is quite evident that the child, if it survives, will be disabled for the rest of its life, and also that the disease most often appears earlier in cases in which its course is severe.

In a classification based on the degree of functional impairment, it follows that any particular case may exhibit different degrees of severity at different periods of his life. The degree of severity to which each case is assigned in this material applies primarily to the condition at the time of the investigation. The previous course of the disease is only of secondary account. It is thus worthy of note that it was by no means always possible to assess the degree of severity on the number of fractures sustained. In several cases only slight impediment of movement remained in spite of a large number of fractures.

In attempting to make a comparison between this material and that of Seedorff, the two milder handicap groups (no and slight handicap respectively) could probably be compared in a general way with Seedorff's type III (osteogenesis imperfecta tarda levis), and the two more severe groups (fairly severe and severe physical handicap) with Seedorff's type II (osteogenesis imperfecta tarda gravis).

As shown in Table 6, the majority of the cases had no (64 %), or, only slight (17 %) impediment in movement, while 19 % of the whole material had a more pronounced difficulty in movement.

It should be pointed out here that physical handicap was primarily used in this report in order to indicate the degree of impediment in movement. As always, in distribution into classes and orders of degree, many cases were difficult to assign to one or the other group. A number of cases, by reason of their mobility and their ability to compensate

TABLE 6. *Distribution of affected individuals according to age and degree of physical handicap*

Degree of physical handicap	Age (years) 1—6	7—14	15—24	≥25	Total No.	%
None	9	24	22	67	122	64.2
Slight	3	1	7	21	32	16.8
Fairly severe	—	2	4	11	17	8.9
Severe	3	4	3	9	19	10.0
Total	15	31	36	108	190	100

their anatomical defects, were placed under the heading of "slight handicap", although it was evident that a patient with the same defects but with a different mental constitution could be assessed as more severely handicapped. Even among those who have no direct impediment of movement and therefore have been classified as having no physical handicap, there are many who have a certain degree of handicap in other respects. The majority of cases thus have to exercise a certain amount of care in order to avoid fractures, and many are of delicate and weak build, which in many respects is prejudicial in normal life (cf. page 180 in socio-medical section).

B. General symptomatology

The syndrome which is associated with the diagnosis osteogenesis imperfecta includes the symptoms of osseous fragility, blue sclerae and impaired hearing. Hyperlaxibility has also often been counted as part of the syndrome. It is very seldom, however, that all the symptoms are found in any particular case. Sometimes the disease is manifested by blue sclerae alone, sometimes only as bone fragility. In this connection reference may be made to the discussion on diagnostic criteria (pages 14—18).

Table 7 shows the extent to which the three main symptoms occur in different combinations in 190 surviving cases of this material.

TABLE 7. *Frequency of different combinations of the three main symptoms: liability to fractures, blue sclerotics and deafness in 190 examined individuals with osteogenesis imperfecta.*

Combinations of symptoms	Males		Females		Both sexes	
	No.	%	No.	%	No.	%
Liability to fractures + Blue sclerae	62	58.5	50	59.5	112	58.9
Liability to fractures + Blue sclerae + Deafness	20	18.9	20	23.8	40	21.1
Liability to fractures + Deafness	2	1.9	1	1.2	3	1.6
Blue sclerae + Deafness	—	—	—	—	—	—
Liability to fractures alone	21	19.8	6	7.1	27	14.2
Blue sclerae alone	1	0.9	7	8.3	8	4.2
Total	106	100	84	100	190	100

TABLE 8. *The frequencies of different symptoms in 190 patients with osteogenesis imperfecta (106 males and 84 females).*

Symptoms	Males		Females		Both sexes	
	No.	Per cent	No.	Per cent	No.	Per cent
Tendency to fractures	105	99.1	77	91.7	182	95.8
Blue sclerotics	83	78.3	77	91.7	160	84.2
Impaired hearing	22	20.8	21	25.0	43	22.6
Hyperlaxibility	46	43.4	39	46.4	85	44.7
Deformities	79	74.5	51	60.7	130	68.4
Abnormal shape of skull	18	17.0	11	13.1	29	15.3
Abnormal ossification	6	(5.7)	7	(8.3)	13	(6.8)
Back troubles	50	47.2	50	59.5	100	52.6
Liability to distortions	30	28.3	36	42.9	66	34.7
Pes plano-valgus	42	39.6	34	40.5	76	50.0
Characteristic dental changes	16	(15.1)	13	(15.5)	29	(15.3)
Arcus corneae	29	27.4	26	31.0	51	28.9
Overliability to bruises	19	17.9	40	47.6	59	31.1

Other symptoms occur more or less associated with the four symptoms mentioned above, for example skeletal deformities, ossification disturbances, delicate body build, dental changes, early appearance of arcus corneae (arcus senilis), and a tendency to subcutaneous bleeding.

Several other anomalies have also been described in osteogenesis imperfecta, such as skin defects, hematological disturbances, and eye anomalies such as myopia and colour blindness and keratoconus. (The literature references are given below together with the descriptions of the various symptoms).

In this study I have attempted to note all the signs and symptoms which occur. Table 8 shows the incidence of the most frequently occurring symptoms and signs in the 190 individuals investigated.

The symptoms observed in the 22 non-surviving individuals (so-called congenital cases) included in the material were as follows:

Symptoms	No. of cases with the symptom indicated
Fractures	22
Fractures localized to	
Upper arms	20
Lower arms	17
Femurs	22
Lower legs	22
Ribs	9
Vertebral compressions	2
Deformities of extremities	21
Ossification disturbances of cranium	17
Colour of sclerae	
Blue	8
White	2
No information	12
Arcus corneae	1
Calcification of arteries of extremities	1

As mentioned, the information concerning these cases was obtained from hospital records, and was thus not based on personal examination.

C. Tendency to fractures

The dominant feature of the disease picture in osteogenesis imperfecta is the idiopathic osseous fragility, with a tendency to fractures. It is this bone fragility which to a great extent determines the degree of severity of the disease.

1. Tendency to fractures in individual cases of different degrees of severity

In the most severe cases of osseous fragility manifested in utero malformations and deformities of the extremities are found at birth. Roentgen examination may reveal both recent and old fractures, often with callus formation even at birth. It has been possible to demonstrate in some cases fractures, callus formation and deformities even in utero (Frerkin and Zink 1952, Poster and Golman 1957, *inter alia*). In cases with the most pronounced bone fragility, fractures can continue to occur after birth due to no other cause than the child's own movements, or to the daily care of the child. In such cases it must be assumed that the prognosis is poor, with a fatal outcome in the majority.

As previously pointed out, the occurrence of one or more fractures and even deformities already at birth, followed by repeated spontaneous fractures, need not necessarily, however, signify an extremely poor prognosis. The stability of the bone tissue seems to be able to increase gradually, the tendency to fractures thus decreasing. Examples of such cases are those described on pages 11—12 in the section on terminology. The lesson to be learnt from these cases, is the importance of avoiding a defeatist attitude in such severe early cases; the best possible fracture treatment should in fact be carried out in order to decrease the risk of deformities.

In those cases who had escaped fractures at birth, it was often seen that they first occurred at about the time when the child began to learn to walk. In several cases the mother described how the child tripped over a mat or a doorstep and fell, breaking a leg or an arm, or related that the fracture had apparently occurred without trauma (e. g. case No. 10:1p, 13:1p, 122:6p). Some parents were not aware that any fracture had occurred, but were able to state that the child had learnt

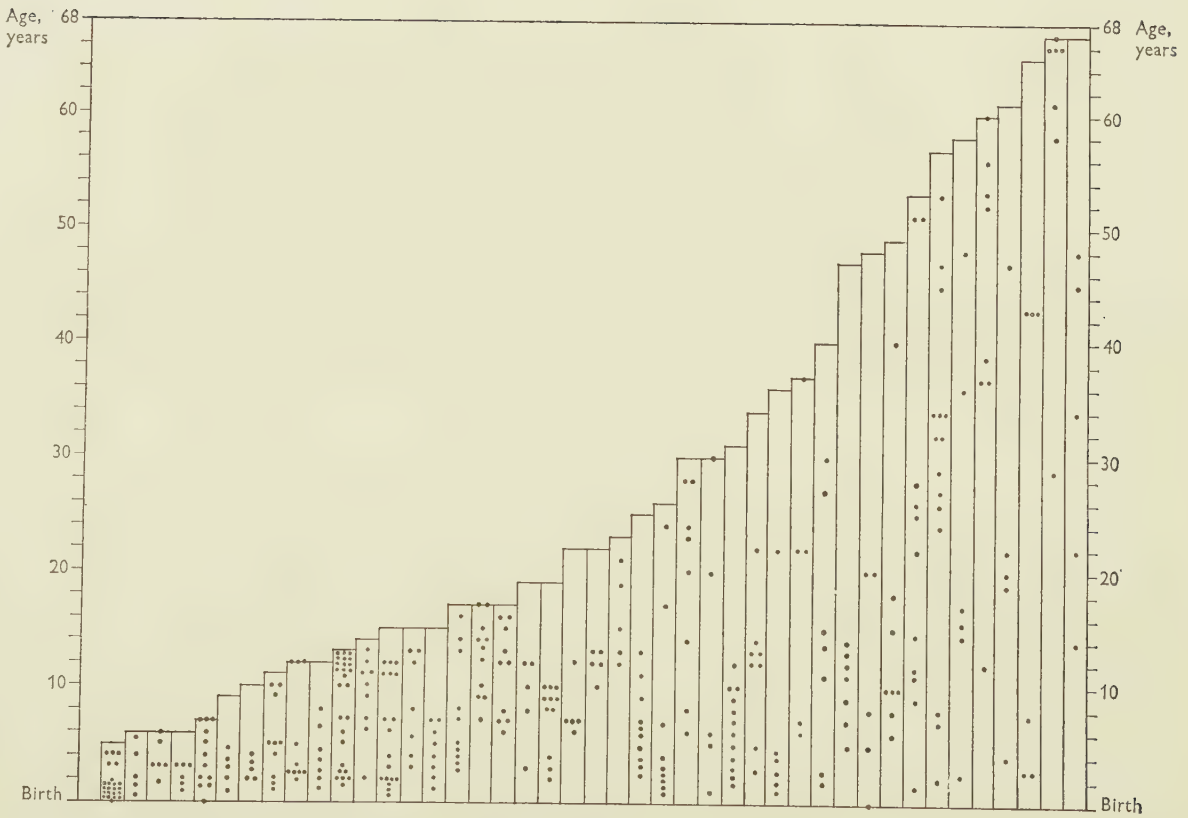

Fig. 1. Age at which fractures occurred in 43 patients of different age, for whom this age was known of all fractures. Each individual is represented by a column and each fracture by a dot.

to walk at the usual time, but suddenly began to avoid standing and reverted to creeping (e. g. case No. 120: 1p).

The majority of the fractures occur during childhood, and greatly decrease in frequency after the age of 15 years, but they may appear later. This will be discussed in more detail below. If the cases are considered individually, it often appears that the fractures occur in periods of up to a few or several years, after which they occur less frequently. This may be observed in several of the cases illustrated in Fig. 1, in which every case is represented by a column and every fracture by a dot. These cases include all those with at least five fractures, for whom definite information regarding the age at each fracture was obtained.

The number of fractures varies greatly from case to case. As shown in Tables 7 and 8, eight cases are included, who, as far as is known, had never had a fracture, but in whom the only sign of the disease was blue sclerae. On the other hand there are several cases who had had 30 to 60 fractures, and one case who had even had 125 fractures.

2. Total number and mean number of fractures

In Table 9 the total number and mean number of fractures in different handicap groups and age groups under 30 years of age are shown. The age classes over 30 years have not been included, as the information concerning these cases was found to be less reliable. In calculating both

TABLE 9. *Number of fractures in osteogenesis imperfecta patients with and without physical handicap in ages under 30 years.*

	Age at examination	No handicap			Handicap			Total		
		No. of patients	No. of fractures	Mean	No. of patients	No. of fractures	Mean	No. of patients	No. of fractures	Mean
Male and female	1— 4	6	15	2.5	1	4	(4.0)	7	19	2.7
	5—14	27	159	5.9	12	198	16.5	39	357	9.2
	15—29	31	183	5.9	20	515	25.8	51	698	13.7
	Total	64	357	5.6	33	717	21.7	97	1,074	11.1

the total and the mean number of fractures for these age groups in the material, an unreasonable result was obtained, namely, that their numbers were considerably lower than those of the younger groups. This is probably due, at least in part, to the difficulty in remembering fractures and visits to doctors caused or made a long time ago, and partly to the fact that medical care in the past offered fewer possibilities of diagnosis and treatment.

More detailed illustration of the significance of bone fragility to these people, and to a certain extent of its cost to the community (e. g. in the form of hospital care in the case of fractures), is given in the report of the socio-medical study.

3. Age at time of first fracture

The age at the time of the first fracture in 100 of the 106 men and in 74 of the 84 women investigated is shown in Table 10. Five men and three women were unable to state when they had their first fracture. A two year old boy and seven women, so far as was known, had never had a fracture (cf. Table 8).

TABLE 10. *Distribution according to age at time of first fracture in 100 males and 74 females.*

Age at 1st fracture	Males		Females		Both sexes	
	No.	Per cent	No.	Per cent	No.	Per cent
At birth	4	4.0	6	8.1	10	5.7
< 1	8	8.0	6	8.1	14	8.0
1— 2	23	23.0	13	17.6	36	20.7
2— 3	18	18.0	13	17.6	31	17.8
3— 4	7	7.0	4	5.4	11	6.3
4 —5	6	6.0	5	6.7	11	6.3
5—10	17	17.0	10	13.5	27	15.5
10—15	10	10.0	10	13.5	20	11.5
15—20	3	3.0	1	1.4	4	2.3
20—60	4	4.0	6	8.1	10	5.7
Total	100	100	74	100	174	100

Fractures had occurred already at birth in 10 of these 174 surviving cases (6 %), and in 14 (8 %) the first fracture occurred during the first year of life. During the second and third years it occurred in no fewer than 67 (almost 40 %) of the cases. In the following years of life the frequency of first fractures decreased. At the age of 15 years the majority, 92 %, had had at least one fracture. There was no great sex difference as regards fracture incidence.

A better estimate of the fracture risk is obtained if this is calculated as a one year risk, i. e. if an estimate is made of the number of individuals who up to a certain age have remained free from fractures, and who incur fractures during the subsequent year. Table 11 is based on such calculations. For both sexes taken together the fracture risk amounts to 8 % in the first year of life, rising to approximately 25 % in the second and third years, and falling again in the fourth and fifth years to 13—15 %, i. e. double the risk of the first year.

The average annual risk for 5-year intervals between the ages of 5 and 20 years is given in the lower part of Table 11. Because of the small number of individuals used for the risk calculation, the figures do not decrease evenly as might be expected. This is particularly evident if the figures for the different sexes are considered. The high figure of

TABLE 11. *Annual frequency of first fractures in different age groups among 96 males and 68 females (cf. Table 10).*

Age, years	Males			Females			Both sexes		
	No. of individ.*	No. of 1st fract.	Per cent	No. of individ.	No. of 1st fract.	Per cent	No. of individ.	No. of 1st fract.	Per cent
0— 1	96	8	8.3	68	6	8.8	164	14	8.5
1— 2	88	23	26.1	62	13	21.0	150	36	24.0
2— 3	65	18	27.7	49	13	26.5	114	31	27.2
3— 4	47	7	14.9	36	4	11.1	83	11	13.3
4— 5	40	6	15.0	32	5	15.6	72	11	15.3
5—10	124	17	13.7	112	10	8.9	236	27	11.4
10—15	66	10	15.1	62	10	16.1	128	20	15.6
15—20	23	3	13.0	31	1	3.2	54	4	7.4
20—60	78	4	(5.1)	116	6	(5.2)	194	10	(5.2)

* in age groups 5—10, 10—15 etc. No. of years of risk.

13.7 % for boys of 5—10 years, compared with the corresponding figure for girls (8.9 %) is, however, due to the relatively high number of fractures in boys 6—7 years old. Of 31 boys entering their sixth year, no fewer than 10 had their first fracture before the age of 7 years. The corresponding figure for girls is 4 out of 26. Thus for both sexes combined the total figure of 14 out of 57 is obtained for ages 6—7 years, i. e. 25 %. The corresponding average percentage figure for the four age years 5—6 and 7—10 is only 7 %. The increased frequency of first fractures at about 6 years, particularly in boys, is too high to be due to random variation alone, and is in this case probably true.

Age at first fracture in different handicap groups. It is evident from Table 12 that there is a connection between the age at the time of the first fracture and the degree of severity (assessed by degree of handicap). There is a significant difference between the two distributions ($P<0.001$). A first fracture before the age of one year is more common in the severely handicapped individuals than in the others. It is also clear, however, that early occurrence of the first fracture is not always connected with a severe course of the disease, or late occurrence with a mild course. This has been mentioned previously in the discussion on the classification based on the degree of severity.

TABLE 12. *Age at first fracture in two handicap groups (100 males and 74 females).*

Age at 1st fracture	No handicap or slight handicap		Fairly severe or severe handicap	
	No. of individ.	Per cent	No. of individ.	Per cent
At birth	4	8	6	36
< 1	7		7	
1— 3	52	38	15	42
3— 5	18	54	4	22
5—10	26		1	
10—15	18		2	
≥ 15	13		1	
Total	138	100	36	100

The salient points concerning the occurrence of the first fracture at different ages may be summarized as follows:

1. there is a maximum in the second and third years of life, and an increase is also evident at 6—7 years;
2. by the age of 15 years the majority (92 %) of both sexes have had at least one fracture;
3. the earlier the occurrence of the first fracture, the greater seems to be the risk of a more severe degree of handicap.

4. The relationship between the number of fractures and the degree of physical handicap

It would be natural to presume that the number of fractures is always proportional to the degree of severity of the disease, and thereby also to the degree of physical handicap. It has, however, been pointed out, in the discussion on the classification according to the degree of severity, that this was not always so. There were, for instance, cases with a large number of fractures, all of which healed well and therefore caused little or no handicap. On the other hand pronounced deformities were to be found in alert, observant patients, who were able to describe how, for example, the lower leg gradually became bent and deformed although this had no direct connection with any fracture (e. g. case No. 37:2p). It is not certain whether this was due to repeated subclinical fractures or to a plastic deformation of the bone.

From these observations, it cannot be accepted as definite that there is any direct relationship between the number of fractures and the degree of handicap, and a further analysis is therefore necessary.

In Table 13, 133 patients (71 men and 62 women) for whom reliable information was obtained concerning the age at each fracture, have been grouped according to the degree of severity and the mean number of fractures per year of observation within different age periods. The small number of individuals with handicap does not permit the division of the material, given in the Table, into different sexes or into very small age classes. Thus in the "slight handicap" group there are 23 cases (14 men and 9 women), in the group with a more severe handicap only 12 cases (6 men and 6 women), and in the group with no handicap 98 cases (51 men and 47 women).

TABLE 13. *Mean number of fractures per year of observation at different age periods among 71 males and 62 females. Both sexes grouped according to degree of handicap.*

Age, years	No handicap			Slight handicap			Fairly severe and severe handicap		
	No. of years of observation	No. of fractures Total	No. of fractures Per yr. of obs.	No. of years of observation	No. of fractures Total	No. of fractures Per yr. of obs.	No. of years of observation	No. of fractures Total	No. of fractures Per yr. of obs.
0— 5	484	131	0.27	114	28	0.25	60	60	1.00
5—15	862	208	0.24	206	53	0.26	91	42	0.46
15—30	863	68	0.08	235	27	0.12	89	14	0.16
30—60	724	34	0.05	278	20	0.07	94	14	0.15

It may be seen in Table 13 that, as expected, those with more severe handicap have on an average a considerably higher frequency of fractures than the unhandicapped individuals. (The frequency in the former cases appears to be 2—3 times higher, but the figures must be regarded with caution, as the individual variation is large and the number of individuals in the group with the more severe handicap is small.) In the first year of life the fracture frequency is especially high in cases with fairly severe or severe handicap. The 12 cases altogether account for 60 fractures during the first five years of life, which means an average of one fracture per individual per year.

In conclusion it may be said, that the degree of physical handicap assessed on the material as a whole is in direct proportion to the fracture frequency. The more severe the handicap, the greater the number of fractures, particularly during the first years of life. The result is in agreement with the relationship between early first fractures and more severe handicap, shown in Table 12.

5. The variation of the fracture frequency at different ages

In calculating the fracture frequency at different ages, only 133 of the total 182 cases with fractures could be used, i. e. the 71 men and 62 women for whom information was obtainable on their ages at the time

of each fracture. This implies a selection, which may affect the representativeness of the material. As previously shown, there is a high correlation between the number of fractures and the degree of handicap. It may also be considered that the age of the patients at the time of the investigation probably affects the number of fractures reported, in that older persons may forget a number of the fractures sustained in their younger years (cf. page 55 and Table 9). The representativeness of this selected part of the material as regards the fracture frequency of the disease must therefore be scrutinized more closely.

In a comparison between the 133 selected cases and all the 182 cases with fractures, the age distributions show satisfactory agreement. A marked difference between the two materials is found, however, as regards the distribution based on the degree of severity of the disease. An estimate of the number of cases in the different handicap classes in the selection material compared with the distribution of the total material shows a marked deficit of fairly severely and severely handicapped cases (12 observed compared with 26 expected cases), and a corresponding excess of those without handicap. This is illustrated as follows:

		No handicap	Slight	Fairly severe	Severe	Total
Males	Obs. No.	51	14	3	3	71
	Exp. No.	42	14	7	8	71
Females	Obs. No.	47	9	2	4	62
	Exp. No.	42	9	5	6	62
Both sexes	Obs. No.	98	23	5	7	133
	Exp. No.	84	23	12	14	133

The deviation is somewhat greater in men than in women. Since a greater number of fractures are on an average followed by a more severe handicap (see Table 13, page 60), it is evident that the selected material which can be used for calculating the fracture frequency at different age periods gives altogether too low values.

This underrepresentation in the selected material of cases with more severe handicap is undoubtedly due to the fact that it was mainly those persons who had sustained a large number of fractures who could not remember when each fracture occurred. They were therefore excluded.

Table 14 shows the variations in the fracture frequency at different ages in the 133 selected cases. The number of fractures has been given in relation to

TABLE 14. *Number of fractures distributed according to age of individual at time of fracture and frequency of fractures as mean number of fractures per year of observation at different age periods in 71 males and 62 females.*

Age, years	Males			Females			Both sexes		
	No. of years of observation	No. of fractures Total	No. of fractures Per yr. of obs.	No. of years of observation	No. of fractures Total	No. of fractures Per yr. of obs.	No. of years of observation	No. of fractures Total	No. of fractures Per yr. of obs.
Under 1	71	4	(0.06)	62	29	(0.47)	133	33	(0.25)
1— 3	142	54	0.38	122	48	0.39	264	102	0.39
3— 5	140	47	0.34	121	37	0.31	261	84	0.32
5—10	331	82	0.25	280	51	0.18	611	133	0.22
10—15	296	121	0.41	252	49	0.19	548	170	0.31
15—20	232	43	0.19	215	11	0.05	447	54	0.12
20—30	373	35	0.09	367	20	0.05	740	55	0.07
30—40	283	17	0.06	254	10	0.04	537	27	0.05
40—60	310	23	0.07	249	18	0.07	559	41	0.07

the number of observation years (the years of risk in each interval of time, i. e. the number of years in which each individual ran the risk of getting fractures). Thereby the effect of the varying age distribution in the patients has been eliminated.

In a comparison with the mean number of fractures in Table 9 a cautious estimate shows that the frequency in Table 14 is probably only half of the actual value, i. e. that value which would have been obtained if the whole of the material investigated could have been included in the calculation.

If, however, it is assumed that the fractures of those cases which were excluded from the calculation were distributed approximately among the same ages as the cases included in Table 14 (which is probably valid; except for the difference that there may be more fractures per person), the figures in Table 14 should be generally applicable, i. e. the variation in the figures with age can be assumed ro reflect the actual variation in the fracture frequency at different age periods.

It must be stated, however, that the figures 0.06 for males and 0.47 for females under the age of one year are misleading. Among the cases which had to be excluded are 9 males with at least one fracture before the age of one year, but only 3 females with one fracture before that age. Also, of the 29 fractures before the age of one year in females, no fewer than 17 fractures belong to one particular individual, all of whose fractures had been recorded from birth. With this information the figure for males can be calculated as 0.16 and that for females as 0.24.

Since as large a fraction as 133 of the total number of 182 investigated cases of osteogenesis imperfecta with fractures are included in these calculations, it would seem valid, with the reservations mentioned above, to conclude that the figures in Table 14 give a good idea of the relative distribution of the fractures at different age periods. This is also supported by the agreement shown between Tables 14 and 11, which indicates the risk for the first fracture at different ages.

Just as the risk for the first fracture, according to Table 11, is greatest during the second and third years of life, when it is approximately double that during the fourth and fifth, the highest frequency as regards the total fractures is also found in the second and third years, according to Table 14. A frequency peak which is almost as high is, also, found in the fourth and fifth years of life. This must be due to the fact that fractures No. 2, 3 etc. have been added on to the first fractures. After the fifth year of life the frequency appears to decrease gradually, and then to increase again in boys towards the age of 15 years, when it is approximately the same as in the 2nd and 3rd years of life. After this age there is a further gradual decrease in the fracture frequency. The frequency figures for females are somewhat lower than those for males after the 5th, and possibly after the 3rd, year of life, and do not show any definite rise at ages 10—15 years, but otherwise they follow the same course, on the whole, as the frequency figures for males.

6. The site of the first fracture

Information on the site of the first fracture was obtained for 172 of the 182 individuals with fractures included in the material. The frequency of the various fracture sites is shown in Table 15. On the left hand side of the Table this is calculated for all the fracture age groups together, and on the right hand side for the fracture age groups 0—2, 2—7 and over 7 years, respectively.

From a calculation on all the first fractures in the material, it is shown that in both men and women the first fracture affects the lower extremities in two cases out of three.

If the fractures are divided into different age groups, it is found that the first fracture is predominantly in the lower extremities up to the age of 7 years (approximately 75 %). After that age the majority occur

TABLE 15. *Localization of first fracture in males and females, and age at its occurrence in 98 males and 74 females (cf. Table 10).*

Localization of first fracture	Males		Females		Both sexes		according to age at first fracture					
							< 2		2–7		7 and over	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Upper extremities:	39	39.8	20	27.0	59	34.3	13	22.4	17	24.3	29	65.9
Clavicle and scapula	5	5.1	5	6.8	10	5.8	1	1.7	4	5.7	5	11.4
Humerus	3	3.1	—	—	3	1.7	2	3.4	—	—	1	2.3
Elbow (incl. olecranon)	11	11.2	2	2.7	13	7.6	2	3.4	4	5.7	7	15.9
Forearm	15	15.3	7	9.5	22	12.8	5	8.6	7	10.0	10	22.7
Hand and fingers	3	3.1	4	5.4	7	4.1	1	1.7	—	—	6	13.6
Arm (more exact site not known)	2	2.0	2	2.7	4	2.3	2	3.4	2	2.9	—	—
Lower extremities:	59	60.2	51	68.9	110	64.0	44	75.9	53	75.7	13	29.5
Pelvic bones	—	—	1	1.4	1	0.6	1	1.7	—	—	—	—
Femur (incl. femoral neck)	22	22.4	18	24.3	40	23.3	20	34.5	15	21.4	5	11.4
Knee	—	—	3	4.1	3	1.7	—	—	—	—	3	6.8
Lower leg	24	24.5	23	31.1	47	27.3	13	22.4	30	42.9	4	9.1
Foot and toes	3	3.1	3	4.1	6	3.5	2	3.4	3	4.3	1	2.3
Legs (more exact site not known)	10	10.2	3	4.1	13	7.6	8	13.8	5	7.1	—	—
Other localizations:												
Skull	—	—	1	1.4	1	0.6	1	1.7	—	—	—	—
Spine	—	—	—	—	—	—	—	—	—	—	—	—
Ribs	—	—	1	1.4	1	0.6	—	—	—	—	1	2.3
Sternum	—	—	1	1.4	1	0.6	—	—	—	—	1	2.3
Total	98	100	74	100	172	100	58	100	70	100	44	100

in the upper extremities (approximately 65 %). These differences are statistically significant.

Only exceptionally have first fractures been recorded elsewhere than in the extremities.

The most common fracture sites in the lower extremities are the femur and lower leg, which are affected to an approximately equal extent.

In the upper extremities the majority of first fractures occur in the lower arm, in both sexes. The next most predominant position is the elbow, in men, and the shoulder girdle in women. At the elbow it is mainly the olecranon process which is fractured, and in the shoulder girdle, the clavicle. The highest frequencies of first fractures in these upper extremity sites occur above the age of 7 years.

In the lower extremities femoral fractures are the most common below the age of 2 years, and lower leg fractures for ages 2—7 years. The difference is significant ($0.02<P<0.05$).

7. Distribution of all fractures on the basis of site

It was possible to record the site of all fractures in 73 of the 105 men and in 66 of the 77 women with fractures. These 139 cases constituted 76 % af the 182 cases who had had fractures. Those particular individuals who had had the greatest number of fractures, also had the most difficulty in recalling the locality of each fracture. There is therefore a tendency to a selection of cases with, on an average, a lower number of fractures. As the number of fractures shown in Table 16 is relatively large (801), the data presented here seem sufficient to give a good idea of the mutual relationships between fractures of different sites. (33 fractures, of which memory could not localize more precisely than "arm" or "leg", have been omitted from the Table.)

The distribution of all extremity fractures, on a site basis, shows good agreement (see Table 16) with the first fracture site (Table 15). This applies to adults of both sexes.

As with first fractures, fractures elsewhere than in the extremities are few. Although no costal first fractures were recorded, they did however constitute 4.5 % of the total fractures (36 cases). Vertebral fractures were only recorded in 1.1 % (cf. section on deformities, p. 81).

TABLE 16. *Distribution of all fractures according to localization in 73 males and 66 females.*

Localization of fractures	Males		Females		Both sexes	
	No. of fractures	%	No. of fractures	%	No. of fractures	%
Upper extremities:	178	38.3	120	35.7	298	37.2
Shoulder girdle and shoulder joint	22	4.7	14	4.2	36	4.5
Humerus	16	3.5	17	5.1	33	4.1
Elbow (incl. olecranon)	47	10.1	13	3.9	60	7.5
Forearm	64	13.8	44	13.1	108	13.5
Hand and fingers	29	6.2	32	9.5	61	7.6
Lower extremities:	263	56.6	192	57.1	455	56.8
Pelvic bones	2	0.4	6	1.8	8	1.0
Femur (incl. femoral neck)	134	28.8	76	22.6	210	26.2
Knee	9	1.9	21	6.2	30	3.7
Lower leg	102	21.9	69	20.5	171	21.3
Foot and toes	16	3.5	20	6.0	36	4.5
Other localizations:	24	5.2	24	7.1	48	6.0
Skull	—	—	2	0.6	2	0.2
Spine	2	0.4	7	2.1	9	1.1
Ribs	22	4.7	14	4.2	36	4.5
Sternum	—	—	1	0.3	1	0.1
Total	465	100	336	100	801	100

Table 16 shows that for both sexes combined, 57 % of the total fractures affect the lower extremities, 37 % the upper extremities, and 6 % other sites, mainly the ribs. The distribution into these three sites is approximately the same for males and females; the difference is not significant.

The commonest sites of fracture are the femur and femoral neck (26 %) and the lower leg (21 %). Next follow fractures in certain parts of the upper extremities, such as the lower arm (13.5 %), the elbow and the bones of the hand (each about 8 %).

There are certain differences between the sexes regarding elbow and hand fractures. In men, no fewer than 26 % (47/178) of the upper

extremity fractures were near the elbow, mainly, as mentioned previously, in the olecranon process. The corresponding figure for women is 11 % (13/120). This difference is significant ($P<0.01$). With the lower extremity, fracture of the femur is more common in men (51 %; 134/263) than in women (40 %; 76/192); this difference is also significant ($P<0.01$). The higher frequency of these fractures in men is offset by a higher frequency of fractures of the upper arm, the bones of the hand and the knee joint in women. With regard to the selective nature of the material the figures given above should be viewed with a certain degree of caution. It seems probable however that a larger material with complete records of all the fractures would show that at least the fractures of the knee joint and the bones of the hand are somewhat more common in women than in men.

Right and left sided fractures. It might perhaps be expected that the fracture risk would be the same for the extremities of the right and the left sides. The following frequency figures were found in the present material. Only those cases were included for whom there was definite information concerning right- and left-sided fractures.

	Men		Women	
	Number of fractures	Of which right-sided	Number of fractures	Of which right-sided
Upper extremities	131	59 = 45.0 %	88	41 = 46.6 %
Lower »	157	98 = 62.4 %	148	70 = 47.3 %

In neither men nor women does the frequency of right sided fractures (45—46 %) deviate significantly from 50 %, as regards the upper extremities. This also applies to the lower extremities in women (47 %). On the other hand there is a significantly greater risk of fractures of the right leg in men (62 %; $P<0.01$).

8. The fracture sites in different handicap groups

Table 17 shows the distribution of the fractures based on locality, with the material divided into two large groups according to the degree of handicap. No significant difference was found between the groups "no handicap" and "slight handicap" as regards the distribution of the fracture sites. They have therefore been combined into one group. The same applies to the groups "fairly severe handicap" and "severe handicap", which have also therefore been united.

It may be seen in the Table that fractures of the lower extremities are much more common in cases with more severe handicap than in those with slight or no handicap.

TABLE 17. *Distribution of all fractures according to localization in two handicap groups in 73 males and 66 females.*

Localization of the fractures	No or slight handicap		Fairly severe or severe handicap		All cases	
	No. of fractures	%	No. of fractures	%	No. of fractures	%
Upper extremities:	263	43.4	35	18.0	298	37.2
Shoulder girdle and shoulder joint	31	5.1	5	2.6	36	4.5
Humerus	20	3.3	13	6.7	33	4.1
Elbow (incl. olecranon)	59	9.7	1	0.5	60	7.5
Forearm	99	16.3	9	4.6	108	13.5
Hand and fingers	54	8.9	7	3.6	61	7.6
Lower extremities:	306	50.5	149	76.4	455	56.8
Pelvic bones	8	1.3	—	—	8	1.0
Femur (incl. femoral neck)	94	15.5	116	59.5	210	26.2
Knee	25	4.1	5	2.6	30	3.7
Lower leg	148	24.4	23	11.8	171	21.3
Foot and toes	31	5.1	5	2.6	36	4.5
Other localizations:	37	6.1	11	5.6	48	6.0
Total	606	100	195	100	801	100

Of the fractures of the lower extremities, femoral fractures (including femoral neck fractures) are also far more common in the group with the more severe handicap. On the other hand, the lower leg fractures are considerably more common in the group with very slight or no handicap. These differences are significant and are found in both sexes.

Of the fractures of the upper extremities, the upper arm is the more common site in the group with more severe handicap. This difference is significant. It is mainly the women who contribute to the high frequency of upper arm fractures in this handicap group. In the group with slight or no handicap, the lower arm and elbow are the most common sites in the upper extremities, in both men and women.

Discussion of fractures

a) The variation of the fracture frequency at different ages

Many authors, including Seedorff, have reported that the tendency to fractures decreases at 15—25 years. The majority consider this to be due to a stabilization of the bone tissue commencing at this time. Seedorff, however, questions this, and maintains that in his experience "the disease does not tend to healing, and the occurrence of secondary or late signs and symptoms likewise go against the theory of healing". He says that he is "inclined to ascribe this restitution to a self-taught attention guarding the patients against injuries, so that it may seem as if the osseous system has become more resistant".

Table 11 (the annual frequency of first fractures at different ages) shows that the fracture risk is at a maximum in the 2nd and 3rd years of life. The risk then decreases, but rises again, both at 6—7 years (higher for boys than girls), and at 10—15 years. Table 14, giving the variation of the frequency of all fractures at different ages, also shows a maximum in the 2nd and 3rd years of life, and another maximum at 10—15 years, the latter being especially pronounced for boys, whilst less certain for girls.

The fracture frequency greatly decreases especially after the age of 20 years in men, and earlier, after the age of 15 years, in women. In the first 3—5 years it is approximately the same both for boys and girls, after which it is lower for females than for males.

It seems reasonable to presume with Seedorff that a large proportion of these variations in the fracture frequency are due to the different degrees of activity in individuals at different ages. The higher frequency of fractures in the 2nd and 3rd years of life thus coincides with the period during which the child learns to walk. The fracture frequency then decreases somewhat in the 4th and 5th years of life, when the child gets steadier. The rise in the frequency of first fractures, observed at 6—7 years, and especially in boys, may be considered as being due to increased activity and increased risks associated with the beginning of school age. The increase in the number of fractures in boys of 10—15 years could similarly be explained by the increased risks at play and other occupations at this age. The general decrease in the fracture frequency after the age of 15—20 years could be due to the fact that the majority have by this time learnt to take care and avoid risks. It is probable that these exogenous factors play at least some role. This supposition is also perhaps supported by the sex difference. Thus while no difference could be demonstrated up to 3—5 years, subsequently the fracture frequency for girls is considerably lower than for boys. From the age of 5 years the male, in play and in other occupations, begins to be more subject to trauma than females. This predominance in males agrees with the findings of Berfenstam et al. (1957) who, in an investigation on accidents in children from birth to 15 years, found a marked predominance in boys for both slight and severe accidents. This was most pronounced for severe accidents. A comparison with these observations on children would seem to be valid, since the majority of the fractures in osteogenesis imperfecta occur before the age of 15 years.

It is also conceivable however that not only exogenous but also endogenous factors may have a varying influence on the osseous tenacity at different age periods, and that changes in these endogenous factors more or less coincide with different periods of activity in the individual. It is known that the endocrine apparatus has normally some influence on osseous formation (cf. McLean and Urist 1955). The growth hormones, gonadotropic hormones, oestrogens and androgens may be mentioned in this regard. It is probable that osseous fragility can be either increased or decreased by endocrinal changes, such as occur during a child's growth periods or at puberty and at the menopause. Certain cases of osteogenesis imperfecta in this series are particularly suggestive of the importance of endogenous factors. Examples of such cases are

those individuals who have obviously tolerated the ordinary strains and trauma of life during their first years without getting fractures, but who later at about 4 or 8 years, or in some cases not until 12 years, without any apparent reason begin to show signs of osseous fragility which would undoubtedly have caused fractures had it existed to the same degree previously. The same applies to the fracture tendency which seems to occur periodically. This periodic tendency is evident in many cases and often cannot be connected with any increased physical strain. In a number of these cases there may be exacerbating factors, e. g. pregnancy, inactivity, nutritional disturbances, and general infections. This will be discussed in more detail later. Finally, it should also be noted that a genetic defect may be such that it does not manifest itself until a certain age is reached.

As regards the decrease in the fracture frequency after the age of 15—20 years, most of the patients in the present material thought that the bone fragility had decreased after a certain age period, and that subsequently fractures were not produced by such a small trauma or strain as would, as a rule, have caused them previously.

To summarize, the following observations seem pertinent. The variation in the fracture frequency which has been shown to exist in different age groups may be explained partly by the different degrees of physical activity and ability to exercise caution, found at different age levels. There are, however, reasons for believing that the bone fragility in itself varies at different ages. It may be assumed that this is due partly to purely endocrinal changes at different stages of development, and partly to other endogenous or exogenous factors, which may have an exacerbating influence on the osteoporotic state. The stabilization of the skeleton, which seems to begin at about the age of 15—20 years, may also be due to the commencement of some maturation of bone formation at that period.

b) The site of the fracture

Both in the case of the first fracture and for all the fractures, it was found that the lower extremity was the predominant site. Of all the first fractures in the material, two thirds had occurred in the lower extremities. Of the total fractures for both sexes combined, 57 % affect-

ed the lower extremities, 37 % the upper extremities, and 6 % other regions, mainly the ribs.

In individuals not suffering from osteogenesis imperfecta the reverse is true, with a marked predominance of fractures of the upper extremities. Berfenstam et al. (1957), in an investigation of childhood accidents in Stockholm in 1955, found that out of 3593 fractures of the extremities, 2733 were located in the upper and 860 in the lower extremities (i. e. a ratio of 3 : 1). This predominance of fractures of the lower extremities in osteogenesis imperfecta as opposed to those in individuals not suffering from the disease, was also found by Schwartz (1933).

This difference in the fracture sites in osteogenesis imperfecta seems to be a good illustration of the inadequate tenacity of the bone in this disease. Normally, exceptionally heavy trauma is required to cause a fracture, and therefore the upper extremities, which may be considered to be most subject to such trauma, are most often affected. In osteogenesis imperfecta, on the other hand, fractures are produced even by strains which the average person experiences in daily life; hence, the lower extremities supporting the whole body weight are more subject to strain, and, consequently, are more often affected.

A frequency distribution of the total fractures on the basis of their occurrence in different skeletal parts shows that femoral fractures (including femoral neck fractures) are the most common (26 %), followed next by lower leg fractures (21 %), and then by fractures of the lower arm (13.5 %), the elbow (8 %), and the bones of the hand and fingers (8 %). This distribution between different fracture sites can possibly be interpreted in the same way as that between fractures of the lower and the upper extremities, discussed above, i. e. that it is those parts most subject to the ordinary strains of daily life that are most often affected by fractures in osteogenesis imperfecta. The sex difference observed as regards certain fracture sites is of interest if regarded in this light. Elbow fractures are significantly more common in men than women, and similarly femoral fractures. On the other hand upper arm fractures and those of the knee joint and hand are more common in women. This could possibly be an expression of the different degrees of strain on different parts of the skeleton in men and women.

As regards right and left sided fractures, a significantly greater risk could only be demonstrated for fractures of the right lower extremity

in men. It is doubtful whether this means that the right leg carries more strain in men, but not in women, and that both the upper extremities are equally subject to strain. Studies on a larger material would possibly throw more light on this point.

If it is accepted that those skeletal parts which are ordinarily subjected to the greatest strain, are affected by the greatest number of fractures, it may be wondered why vertebral fractures so rarely appear in the records of the material. This is probably due to the fact that vertebral compressions take place more imperceptably, and are not therefore noted. This is supported by the fact that the frequency of spinal deformities, as will be shown later, is of the same order of size as that of the total fractures of the lower and upper extremities respectively (see Tables 20 and 23).

c) The sites of fractures in different handicap groups

Since the degree of handicap may be regarded as an expression of the degree of bone fragility and it may be presumed that the lower extremities carry more strain than the other parts of the body, it seems reasonable (see above) that the percentage of fractures of the lower extremities is higher in the group with a more severe handicap.

The strong predominance of femoral fractures over fractures of the lower leg in the group of more severe handicap is, however, worthy of observation (Table 17). It is relevant to ask whether femoral fractures in themselves give rise to a greater risk of disablement than fractures of the lower leg and other parts in general. In order to throw more light on this question reference may be again made to Table 15 (page 64), concerning the first fracture with respect to its site, and the age at which it occurred, for 172 of the 184 cases who had sustained fractures.

This material includes 169 first fractures of the extremities, and of these, 87 (51.5 %) consisted of femoral and lower leg fractures. This figure agrees well with the corresponding figure for the 139 cases, for whom information was obtained concerning the sites of all fractures (Tables 16 and 17). Of these, 50.6 % (381/753) of all fractures of the extremities consisted of femoral and lower leg fractures. The distribution of the 87 cases whose first fractures were of the femur or lower leg, based on the site and age at the time of fracture, is as follows:

	<2 yrs.	2 yrs. and over	Total
Femoral fractures	20 = 62 %	20 = 37 %	40 = 46 %
Lower leg fractures	13 = 39 %	34 = 63 %	47 = 54 %
Total	33 = 100 %	54 = 100 %	87 = 100 %

As mentioned on page 65, there is a significant difference between femoral and lower leg fractures in the distribution based on the age at the occurrence of the fractures ($0.02 < P < 0.05$). Femoral fractures are more common than fractures of the lower leg in the first two years of life. It can be shown that this difference is even more pronounced, if at the same time the handicap is taken into consideration ($P < 0.01$), i. e. the difference is greater with increasing degree of handicap.

The relationship between the degree of handicap and the age at the time of the first fracture is especially striking in femoral fractures. This relationship is probably also found, however, in other fractures, as may be seen in Table 18. This Table shows the distribution of cases based

TABLE 18. *Distribution of 169 cases according to age at first fracture of extremities and degree of physical handicap (98 males and 71 females)..*

Localization of first fracture	Degree of phys. handicap		Age at first fracture		Total
			under 2 yrs.	over 2 yrs.	
Femur (incl. femoral neck)	None or slight	No.	7	15	22
		%	32	68	100
	Fairly severe and severe	No.	13	5	18
		%	72	18	100
Other localization (than femoral) of the extremities	None or slight	No.	29	83	112
		%	26	74	100
	Fairly severe and severe	No.	8	9	17
		%	47	53	100
	All cases	No.	57	112	169
		%	34	66	100

on the age at the first fracture combined with the degree of handicap, both for femoral fractures and for other fractures of the extremities. No fewer than 72 % of the cases with a more severe handicap had a fractured femur as the first fracture before the age of 2 years. The corresponding percentage figure for those with slight or no handicap is only 32 %. The difference is significant ($0.01 < P < 0.02$). In the group with other fractures of the extremities, 47 % of the cases with more severe handicap had the first fracture before the age of 2 years. The corresponding figure for those with slight or no handicap is 26 %; in these latter groups a certain degree of levelling has taken place, but there is a slight tendency to difference ($P \simeq 0.05$). This supports the view that several fractures at an early age, regardless of site, indicate a more pronounced bone fragility with a consequent risk of handicap. Even if femoral fractures before the age of 2 years are strongly dominant in the most severely handicapped, this cannot therefore be regarded as evidence that the femoral fractures in themselves give a greater risk of disablement than fractures of other localities.

It is probable that the more pronounced the bone fragility, the greater is the risk of fractures in those sites which are especially subject to strain.

d) Special fracture sites

It has been reported by other authors that the femur is the most common fracture site. Key (1926) thus states "that European investigators believe that the femur is the bone most frequently broken", and Holcomb (1931) "that there is no doubt that the femur is fractured more often than any other bone".

The relatively high frequency of fractures in the elbow region, of which a large proportion consists of olecranon fractures, has been discussed by many authors (Bronson 1917, Schwarz 1933, Seedorff 1949 and others). Ekman, as early as 1788, observed in one of his patients "that the ulna has been broken close to the elbow, which therefore cannot be extended without difficulty". This type of fracture, and also vertebral compression, probably occurs more often than is observed. In the present material some deformities of the elbow were observed, indicating old olecranon fractures of which the patients had no knowledge.

Some authors have believed that certain sites were predilection regions to fracture in some cases, and sometimes even in several cases within the same family. Stewart (1922) thus found in one family a predominance of right sided fractures. Axman (1831) also found it strange that, of the total 14 fractures which he and his brothers had had, 11 were right sided and only 3 left sided.

Davenport and Conard (1915) state: "The commonest bone to break is the femur. But in some families the humerus seems especially weak and in still others the clavicle is frequently broken."

No individuals or families with predilection regions of this sort have been observed with certainty in the present material. One 19 year old male (case No. 120:1p), whose numerous fractures occurred in the metacarpal and metatarsal bones and the bones of the fingers, could possibly be placed in this category. However, he had also had a fracture of the right elbow, and exhibited sabre-shaped curvature of the lower arms and lower legs.

e) Are fractures in osteogenesis imperfecta less painful than other fractures?

A number of authors (Key 1926 and others) have stated that it is characteristic of fractures in osteogenesis imperfecta that they cause very little pain. Others, including Blencke (1924) conclude, on the other hand, that the fractures are associated with a great deal of pain. Seedorff (1949) found that the degree of pain varied, and was dependent on the severity of the injury which caused the fracture, and also on the emotional stability of the patient. Due to this divergency of opinion, a number of the patients in the present material were asked about the painfulness of their fractures. The information obtained, however, did not indicate either that the fractures were particularly painless or unusually painful.

A woman (case No. 10:Mp), who had had eight fractures, stated that in each instance she had experienced intense pain at the actual time of fracture, but that the pain had lessened afterwards, to return only with movement at the fracture site. Her 7 year old son (No. 10:1p) used to complain of pain at the time of fracture and during the following few hours. A 61 year old man (case No. 23:1p) stated that he had an insignificant amount of pain at the actual

time of fracture, but that most of the pain occurred after about 2 hours, associated with the swelling. A 26 year old man (case No. 30:Fp), who had sustained about 60 fractures, said that he did not feel very intense pain at the time of fracture, but that most pain occurred later with the movements necessary while being taken to the doctor, and during treatment, etc. This, together with the knowledge of the length of time which each fracture involved before recovery and before the restoration of full working ability, caused the patient more and more suffering with each new fracture.

The impression obtained from the present material is thus that the fractures in osteogenesis imperfecta do not differ to any significant degree, as regards pain, from those in individuals not suffering from the disease.

f) The healing of fractures in osteogenesis imperfecta

Gurlt (1862), Spurway (1896) and Bronson (1917), and several later authors have maintained that the fractures in osteogenesis imperfecta heal remarkably quickly. This has also been found in many cases in the present material; the doctors treating these cases have given information to this effect, and the patients themselves had the general impression that healing took place unusually rapidly. To obtain a more objective verification it was considered of value to make an analysis of the length of the period of medical care, in order to obtain some idea of the period of care needed for fractures of different types. It is evident, however, at least as far as this material is concerned, that the patients were treated under such varied conditions, and by so many different doctors, that the conditions of treatment would show far too great an intrinsic variance for any conclusions on the course of healing to be drawn from such an analysis. The information from authors, doctors in charge of cases, and patients is, however, in such good agreement that a definite impression is obtained that the healing of fractures in osteogenesis imperfecta often takes place unusually rapidly.

1. The liability to fractures can show all grades of variation, from cases who have had numerous fractures already before and at birth and who are unable to survive, to those who only have occasional fractures, or, no fractures at all. In the severe cases it cannot always be determined at a very early age whether the child will survive or not; it is therefore important that the treatment of the fractures should always be carried out even in the most severe cases with all possible care in order to minimise the risks of deformities.

In the individual case the fractures often occur periodically.

2. The majority of the fractures occur in the 2nd and 3rd years of life, where there is a frequency peak. The fracture frequency then decreases somewhat, but at the age of 6—7 years there is again an increased risk, greater for boys than girls, and similarly at 10—15 years, especially pronounced for boys and less certain for girls. From the ages of 15—20 years the fracture frequency is greatly reduced both for men and women. In the first 3—5 years it is approximately the same for boys and girls, after which it is somewhat lower for the female than for the male sex. The variation in fracture frequency thus observed at different ages can presumably be due partly to extrinsic factors such as the varying physical activity and different degrees of caution exercised at different ages, and partly to an intrinsic variation of the bone fragility at different ages. This variation in the degree of bone fragility may be due partly to purely endocrinal changes at different stages of development, and partly to other endogenous or exogenous factors which may have an exacerbating influence on the osteoporotic state. It is possible that some maturation of the defective bone formation occurs at 15—20 years, when a stabilization of the skeleton may be observed.

3. Cases of osteogenesis imperfecta with more severe handicap have, on an average, a considerably higher number of fractures than cases with only slight or no handicap. The occurrence of the first fracture before the age of 1 year is also found to a greater extent in the more severely handicapped cases than in those with a lesser degree of handicap.

4. While in individuals not suffering from osteogenesis imperfecta, upper extremity fractures are far more common than those of the lower extremities, in this disease the reverse is found. In the study of those

cases (139 individuals) for whom the locality of all fractures could be recorded, it was found that 26 % of the fractures affected the femur (including the femoral neck), 21 % the lower leg, 14 % the forearm, 8 % the elbow and 8 % the bones of the hand. Certain differences between the sexes are shown.

5. It is reasonable to expect, in the individual cases, that the fractures most often occur in the above mentioned order. This view is supported by the fact that femoral fractures as first fractures occur, on an average, at an earlier age than lower leg fractures; also that lower extremity fractures occur earlier than those of the upper extremities.

6. Those children who commence having fractures before the age of 2 years run a greater risk of later becoming handicapped by the disease. Since femoral fractures are strongly dominant before that age, more fractures of the femur are found, on an average, in the most severely handicapped than in the other handicap classes. This does not mean, however, that an early femoral fracture will in itself, necessarily, cause permanent handicap. It is probable that the occurrence of several fractures at an early age, regardless of locality, indicates a more pronounced osseous fragility with a subsequent risk of handicap.

7. A strong relationship has been demonstrated between the degree of handicap on the one hand and the number of fractures and the age at the time of the first fracture on the other. This supports the view that the principles used in this investigation for assessing the degree of handicap may be considered satisfactory for measuring the severity of the disease.

D. Skeletal deformities

It seems reasonable, on the basis of the frequently recurring fractures alone, to expect skeletal deformities in a condition such as osteogenesis imperfecta. Certain observations support the view that deformities may also occur to a not insignificant extent as a result of an increased plasticity of the defective osseous tissue. This matter will be further discussed later in this section.

The diagnosis of a skeletal deformity has been based on the external examination, supplemented in a limited number of cases by X-ray

evidence. Deformities of the skull and the bones of the extremities were stated as existant, when they were demonstrable with certainty by means of inspection and palpation. Marked scoliotic or kyphotic curvatures, or shortening of the back suggestive of changes in the vertebral bodies, were denoted as deformities of the back. It would have been of interest, particularly in regard to spinal deformities, to have had X-ray examinations in each case. It seems most probable that a greater number of deformities would then have been revealed. In several of the small series of cases previously examined radiologically, deformities which would otherwise have remained undiscovered were revealed (e. g. cases No. 43 : 2p, and No. 102 : 4p). For practical resons, however, such a systematic X-ray examination was not considered feasible within the scope of this investigation.

In the following sections, the types and sites of predilection of the different skeletal deformities are first described, and an analysis of the relative occurrence of spinal and extremity deformities with regard to sex, site, different handicap groups and different age groups follows.

This analysis follows in general the same lines as that of the fractures. It is unfortunately unavoidable, therefore, that certain aspects discussed in the fracture section will be repeated in the discussion of the deformities.

1. Deformities and disturbed ossification of the cranial bones

Vrolik (1849) discussed certain deformations and ossification disturbances in the cranial bones in the one fatal case of osteogenesis imperfecta which he described. Preiswerk (1912) gave a detailed description of extreme ossification disturbances in the skull bones in a surviving case. Bronson (1917) observed that changes of this type had nothing to do with hydrocephaly. He also pointed out that this ossification disturbance and skull deformation is not only found in the so-called congenital cases, which have fractures already at birth, but, also, in surviving cases, whose fractures do not occur until later.

The picture of ossification disturbances and cranial deformities, described by previous authors, has been corroborated in a study of the present material. In 12 of the 22 lethal cases, it was reported that the skull felt membranous to a greater or lesser extent. In 12 cases the ossi-

fication had only taken the form of scattered bone islets, and in 12 cases the fontanelles and sutures were increased in breadth. Disturbed ossification had been observed in a total of 17 of the 22 cases (cf. page 52). Among the 190 surviving cases investigated, ossification changes, of the same type as those found in the lethal cases, were demonstrated at birth in 13 cases who were examined at an early age. It is possible that an ossification disturbance of the same type would have been found in a larger number, if all the cases had been examined at birth.

An abnormal skull shape was found in 29 of the 190 cases examined, more often in the severe than in the slight cases. The characteristic skull deformation is a varying degree of outward bulging of the frontal, temporal and occipital bones. It appears as if the cranium has sunk down over the base of the skull, and spread out towards the sides. It is as if the skull, because of the plasticity of its bones, is re-shaped by its own weight. H. Nielsen has spoken of a "Soldier's helmet skull", and Apert of "crane à rebord". In a 7 year old girl (Case No. 134:1), who exhibited the skull shape described, and who died during an operation, the post mortem examination revealed considerable depression of the base around the foramen ovale.

The occurrence and type of skull deformities support the view that the skeletal deformities in osteogenesis imperfecta cannot only be ascribed to defectively healed fractures, but that they are to no small extent due to an increased plasticity of the defective bone tissue.

2. *Spinal deformities*

While the number of vertebral fractures observed were found to be exceedingly small compared with fractures of the extremities, the deformities of the spine, as will be shown later (Tables 20 and 23), are approximately as common as those of both the upper and lower extremities (cf. pages 65 and 73).

Spinal deformities occur at all ages (cf. Table 23). Typical vertebral body deformities (cf. p. 120 X-ray characteristics) can sometimes be demonstrated radiologically as early as during the infant years (cases Nos. 102:4p and 141:2p). In several cases with pronounced spinal deformities, these have developed without causing pain (e. g. case No.

170 : 1p). In other cases the parents have reported that the children had complained of pain in the back when being pushed in the perambulator, or when being taken by cycle over uneven ground, but that otherwise no spinal symptoms were observed in spite of the fact that the back had gradually become considerably contracted, or deformed in other ways (e. g. case No. 146 : 1p). Even at later ages, when the fracture tendency is in other respects less, a progressive spinal deformation is common. A female patient belonging to the largest family in this material, with a comprehensive knowledge of the disease, observed that those members of the family who had blue sclerae "shrank" more and more with increasing age. Seedorff (1949) made the same observation in his material.

It is remarkable that neurological symptoms are so rare, although there are often pronounced deformities of the vertebral column (cf. "Lower back trouble and other spinal symptoms", below). In the cases examined here, no lasting neurological disturbances, for instance in the form of paresis, could be observed, although special attention was paid to this question. It is possible that this is a demonstration of the great plasticity, characteristic of all osseous tissue, which the osteoporotic bone in osteogenesis imperfecta presumably possesses to a particularly high degree. It is conceivable, in slowly occurring vertebral compressions, that the plastic property of the bone enables the intervertebral foramina to remain large enough for the nerve roots. This might be brought about by means of the counterpressure, which the nerve roots exert on the bone tissue. It is quite likely this plasticity in the bone which causes the vertebral body compressions to develop so insidiously that the patient notices little or nothing of their occurrence.

Lower back trouble and other spinal symptoms. During the investigation the patients were asked whether they had had back trouble in any form, and to what extent. Of the total of 190 cases examined, including both children and adults, 100 (52.6 %) had had more or less pronounced back trouble. Hult (1954) investigated a normal non-selected material of 1193 male workers aged between 25 and 59 years, from different occupational groups. He found that there was a history of insufficiency symptoms, lumbago and sciatica (the lumbar spine syndrome) in 60 per cent of these persons. The incidence was high in all occupational groups, but was definitely higher in those engaged in heavy work (64.4 per cent) than in light occupations (52.7 per cent).

The occurrence of back trouble in the corresponding age groups

(25—59 years) of the individuals examined with osteogenesis imperfecta, is as follows:

	Total No. cases of o. i. 25—29 yrs. of age	Cases with back trouble	
		No.	Percentage
Males	46	25	54.4 ± 7.5 %
Females	43	28	65.1 ± 7.3 %
Both sexes	89	53	59.6 ± 5.2 %

It would seem valid to make a comparison between these figures and those reported by Hult from his material of cases not suffering from osteogenesis imperfecta. It is somewhat surprising to find that subjective back trouble among these cases of the disease is not more frequent (54 % for men and 65 % for women) than that found by Hult in his normal non-selected material.

3. Thoracic and pelvic deformities

Deformation of the thorax most often consists of different forms of asymmetry, secondary to kypho-scoliotic changes in the spine. In a number of cases, thoracic depression of the same type as is found in rickets, may be observed. This appears to be caused by the compliance of the ribs to the negative intrathoracic pressure and to the pull of the diaphragm. Deformities of the pelvis are manifest as different degrees of pelvic constriction, only being considerable in the more severe cases.

4. Deformities of the extremities

The deformities in osteogenesis imperfecta are characterized particularly by curvatures of the long bones. The tibia is often bent with a forward convexity and with flattened sides, presenting the deformity of "tibia en lame de sabre" also described in tardive congenital syphilis. This curvature can vary from a mere suggestion of bending to a curve of more than 90°. The femur is often seen to be bent with a laterally

forward convexity, in extreme cases so pronounced that the femur takes the form of a shepherd's crook. In both the lower arms and humerus there is a convex deformity, most often in a lateral direction.

In addition, other deformities can, of course, occur from badly healed fractures. Decreased mobility of a joint as a result of nearby fractures is not uncommon.

Deformities, like fractures, of the elbow are remarkably common. It has been pointed out previously (p. 75) that elbow deformities indicating old olecranon fractures were observed in several cases without the patient being aware of ever having had a fracture. As may be seen below (Table 25), the percentage of deformities in the elbow exceeds the recorded precentage of fractures at this site. These deformities are probably mainly due to badly healed fractures.

The type of deformities found in the long bones, and also the way in which they progress, support, on the other hand, the view that in many cases at least they are partly a result of plastic deformation of the defective bone tissue, subjected to the strain exerted by both the body weight and muscular activity (cf. Glovers 1922, Scott 1924). As mentioned previously, pronounced deformities were thus found in alert, observant patients who were able to report, for example, how the lower leg had gradually become bent without, to their knowledge, any fracture (e. g. case No. 37:2p). On the other hand there were cases who had had a large number of fractures, all of which had healed well and caused little or no deformity (e. g. No. 30:Fp).

A special type of deformity of the long bones has been described by Fairbank and Baker (1948), *inter alia*, under the name of *hyperplastic callus formation*. They found the following phenomenon in six cases of osteogenesis imperfecta:

a) Formation of intensely calcified local callus, not invariably preceded by a recognizable recent fracture. b) Excessive formation of ossified callus which enveloped the shaft to a varying but quite unusual extent, and in some cases displayed a strong tendency to result in permanent enlargement of the affected bone. Evidence of antecedent fractures of the affected bones was again not invariably apparent in the radiographs. c) Formation of bony excrescences on the shafts of long bones, particularly on the interosseous borders and without the faintest sign of antecedent fractures.

It is evident that deformities of this type are relatively rare in osteo-

genesis imperfecta. Only a few other similar cases have been described. *inter alia* by Brailsford (1943), Apley (1951), Hilton (1953), and Strach (1953).

During the present investigation one individual (case No. 150:2p) was found with enlargement of the left humerus and both femurs, which seems to correspond essentially with Fairbank's description quoted above. This case was discussed in detail by Hessén (1952), and will therefore not be described further here. In such enlargements of the long bones, the possibility of malignant tumors must, of course, be taken into consideration. Hatteland (1957) reported one such malignant case, and at the same time reviewed six previously reported cases.

5. *Occurrence of deformities in males and females at different ages*

As may be seen in Table 19, deformities were observed in 68.4 % of all the individuals examined, probably more often in males than in females ($P \simeq 0.05$). If the frequency is calculated for 105 men and 77 women, i. e. the number of individuals who had had fractures at the time of the investigation (cf. p. 56), the difference between the sexes is found to be somewhat less marked (75.2 % for men, 66.2 % for women and 71.8 % for both sexes combined).

The higher frequency of deformities in males evident in Table 19 appears to be essentially due to the high frequency of deformities in men of 50 years and over. The difference between the frequency in men

TABLE 19. *Patients with skeletal deformities in different age groups.*

Age at observation (years)	Males			Females			Both sexes		
	No. of ind.	with deformities		No. of ind.	with deformities		No. of ind.	with deformities	
		No.	%		No.	%		No.	%
1— 9	11	6	54.5	13	7	53.8	24	13	54.2
10—29	47	34	72.3	26	17	65.4	73	51	69.9
30—49	28	20	71.4	28	16	57.1	56	36	64.3
≧ 50	20	19	95.0	17	11	64.7	37	30	81.1
Total	106	79	74.5	84	51	60.7	190	130	68.4

(95 %) and women (65 %) is statistically significant at these ages ($P<0.02$). All the patients in this age group (20 men and 17 women) had had fractures. In the age group under 10 years there appears to be no sex variation (frequency = 54 %). Above 10 years of age the frequency rises, the increase being considerably greater in males. In males the deformity rate was relatively constant at 72 % up to 50 years, after which it increased significantly to about 95 %; in females, however, the value remained relatively constant at 60 % (65 % if the calculation is made on the number of females with fractures). It seems very probable that these sex differences are dependent partly on the greater fracture risk for males between the ages of 10 and 29 years, and partly on the relatively great risk of deformities after elbow fractures, which are more common in males (see pp. 66—67). It was thus found in a comparison of the distribution of fractures and deformities based on their situation, that in both sexes deformities of the elbow joint were more common than might be expected from the frequency of elbow fractures (see Table 25). The same applies to deformities of the lower leg, but to a lesser extent. As already noted, the type of elbow deformity often indicated earlier olecranon fractures, even if the patient was not aware of this. Lower leg deformities, on the other hand, often displayed an even curvature without direct indication of fracture. In men, these deformities were evenly distributed over all the age groups, whereas in women, deformities of the elbow and lower leg were rarely found over the age of 50 years. The 19 men over 50 years, who at the time of the investigation were found to have skeletal deformities (Table 19), had altogether 23 deformities of the extremities, of which no fewer than 15 were at the elbow joint and the lower leg (9 and 6 deformities respectively). In 11 women, over 50 years old, the corresponding figure was 2 (1 elbow and 1 lower leg deformity) out of a total of 9 deformities of the extremities.

There is a lower fracture risk in females over 5 years of age, particularly in the age group 5—20 years (see Table 14 and p. 63). Since deformities result, at least to a certain extent, from badly healed fractures, it is reasonable to assume that a lower fracture risk should also mean a lower deformity risk. It is thus probable that this at least partly explains the lower incidence of deformities in women.

6. *Distribution of deformities in the upper and lower extremities and spine, in males and females*

In Table 20 the site of the deformities has been classified into three main groups, *viz.* the upper extremities, the lower extremities and the spine. It may be seen in part A of the Table that deformities of both the upper and lower extremities are considerably more common in men (40—50 %) than in women (20—30 %); these sex differences are statistically significant ($P<0.02$). Deformities of the spine, on the other hand, have approximately the same frequency in both men and women (about 40 %).

With such high frequencies it seems natural that different combinations of deformities are quite common (part B, Table 20). The combination of spinal deformities occurring together with those of the lower extremities seems to be the most usual (about 12 % in both sexes), and appears to be somewhat more common than might be expected to occur

TABLE 20. *Patients with deformities of three main anatomical sites.*

Site of deformities	Males (106)		Females (84)		Both sexes (190)	
	No.	per cent of 106	No.	per cent of 84	No.	per cent of 190
A. *Regardless of combined sites:*						
Upper extremities	43	40.6	18	21.4	61	32.1
Lower extremities	48	45.3	24	28.6	72	37.9
Spine	43	40.6	35	41.7	78	41.1
Total No. of sites	134	—	77	—	211	—
B. *With regard to combined sites:*						
Upper extremities only	13	12.3	8	9.5	21	11.1
Lower extremities only	12	11.3	7	8.3	19	10.0
Spine only	11	10.4	16	19.0	27	14.2
Upper + Lower extremities	11	10.4	1	1.2	12	6.3
Spine + Upper extremities	7	6.6	3	3.6	10	5.3
Spine + Lower extremities	13	12.3	10	11.9	23	12.1
Spine + Upper + Lower extremities	12	11.3	6	7.1	18	9.5
Total No. of individuals	79	74.5	51	60.7	130	68.4

at random. The over-representation of this combination is not statistically significant. It seems, however, plausible that a deformity of a lower extremity may, by causing uneven weight-bearing, contribute to the development of a deformity of the spine.

7. *Frequency and site of deformities in different handicap groups*

The incidence of deformities in the different handicap groups was: no handicap 52.5 %, slight handicap 93.8 %, and fairly severe, or, severe handicap 100 % (Table 21). The last value is to be expected.

It may appear curious and perhaps require some explanation that two of the 32 patients who were reported as having slight handicap showed no deformities (Table 22). One of the patients was a 4 year old boy, who, while not exhibiting any definite skeletal deformities, had a pronounced pes plano valgus which somewhat impeded his walking. The other was a 44 year old woman who had neither skeletal deformities nor actual impediment of movement. However, because of extreme deafness she was for the most part unable to work, and therefore, although not satisfying the criteria of handicap used generally in this investigation, she was recorded as being slightly handicapped.

TABLE 21. *Site of deformities in 190 individuals with different degrees of physical handicap.*

Site of deformities	No handicap (122 ind.)		Slight handicap (32 ind.)		Fairly severe and severe handicap (36 ind.)	
	No.	per cent of 122	No.	per cent of 32	No.	per cent of 36
Upper extremities	31	25.4	12	37.5	18	50.0
Lower extremities	16	13.1	21	65.6	35	97.2
Spine	36	29.5	16	50.0	26	72.2
Individuals with deformities	64	52.5	30	93.8	36	100.0
Mean No. of fractures per individuals	5		10		25	

As regards the site of the deformities (Table 21), those of the lower extremities have the closest association with the degree of handicap. Of the 122 individuals regarded as not physically handicapped, only 13 % had deformities of the lower extremities, compared with 97 % in the group with fairly severe or severe handicap. The corresponding difference for the incidence of deformities of the upper extremities and the spine is not nearly as great. According to the criteria which have been used in the assessment of handicap, a close relationship between the degree of handicap and deformities of the lower extremities might be expected. It is of interest to report, however, that no fewer than about a quarter of the cases without handicap showed deformities of the upper extremities or spine, and in several cases a combination of both. In these cases the deformities were relatively slight, neither impeding ordinary movement, nor being troublesome for work or other occupations.

Table 22 illustrates the relationship between the degree of physical handicap and the severity of the deformities. Of those cases without deformities, practically all (58 of 60, or 97 %) had no handicap (cf. above), and of those with fairly severe or severe deformities, 85 % (35

TABLE 22. *Distribution of all the individuals examined (190 individuals) according to degree of physical handicap in different groups as regards severity of deformities. (When an individual had more than one deformity, the degree of severity was recorded as that of the severest one.)*

Deformities		Physical handicap			Total
		None	Slight	Fairly severe and severe	
None	No. of ind.	58	2	0.	60
	per cent	96.7	3.3	0	100
Slight	No. of ind.	64	24	1	89
	per cent	71.9	27.0	1.1	100
Fairly severe	No. of ind.	0	5	8	13
	per cent	0	38.5	61.5	100
Severe	No. of ind.	0	1	27	28
	per cent	0	3.6	96.4	100

of 41) were moderately or severely handicapped. (One man, in spite of a severe spinal deformity, was only relatively slightly handicapped.)

The mean number of fractures per individual is given in the lower line of Table 21. It is found that with an increasing number of fractures the average degree of handicap increases. This is presumably connected with the fact that the risk of severe deformities increases with increasing osseous fragility (cf. below, p. 93 ff).

8. Occurrence of deformities at different sites in different age groups

The overall frequency of deformities in the age group 0—9 years was 54.2 %, and for those over 50 years of age, 81.1 % (see last column of Table 23 and Table 19). The site of deformities has been disregarded here. The increase between 10 and 50 years is not evenly distributed. From 54 (± 10) % under 10 years, the value rises to 73 (± 7) % in the age group 10—19 years. Subsequently, allowing for random variations, the frequency remains relatively constant at about 65 % until in the over 50 age group it rises to 82 (± 6.5) %, due to a great extent to a high frequency of elbow deformities in men in this age group.

As shown in Table 23 the frequency of individuals with deformities of the lower extremities is approximately the same throughout all the

TABLE 23. *Number of individuals with deformities localized to different body-parts in different age groups.*

Age at examination	No. of ind. in the age group (N)	Individuals with deformities of upper extremities		lower extremities		spine		Regardless of locality	
		No.	per cent of N	No.	per cent of N	No.	per cent of N	No.	per cent of N
under 10	24	4	16.7	10	41.7	5	20.8	13	54.2
10—19	44	15	34.1	17	38.6	17	38.6	32	72.7
20—29	29	10	34.5	12	41.4	10	34.5	19	65.5
30—39	31	10	32.3	10	32.3	13	41.9	19	61.3
40—49	25	8	32.0	10	40.0	12	48.0	17	68.0
50 and over	37	14	37.8	13	35.1	21	56.8	30	81.1

age groups, i. e. about 38 (± 3.5) %. The incidence of cases with deformities of the upper extremities and/or spine (regardless of any possible combination with deformities in the lower extremities) increases from 33 % (8 out of 24) in the age group 0—9 years to 64 % (28 out of 33) in the age group 10—19 years. This latter increase of 31 % is significant ($P<0.02$).

As shown earlier (p. 63) fractures of the lower extremities usually occurred earlier than those of the upper extremities. The fact that this was also true for the deformities seems to lend support to the view that they are to a great extent secondary to fractures. Increased plasticity must however, also be taken into account as a cause of deformity, and it seems reasonable to suppose that, having to support the weight of the body from an early age, the lower extremities would be exposed to greater and earlier strain than the upper extremities. It is thus probable that both fractures and increased plasticity of the bone tissue are causative factors acting either independently or in combination.

While fractures of the vertebrae were rarely recorded (1.1 %) (see Table 16), the frequency of deformities of the spine was approximately the same as that of the upper and lower extremities respectively (Tables 20 and 23). This may be due partly to the fact that a number of vertebral fractures occurred so imperceptably as to remain unobserved, and partly to a gradually progressing plastic deformation of the vertebrae. While the frequency of deformities of the extremities is relatively constant in the age groups over 10 years, the frequency of spinal deformities appears to increase progressively with increase in age (see Table 23).

9. The site of the deformities in different skeletal parts

The actual and percentage numbers of cases with deformities at different anatomical sites are given in Table 24. In this connection, deformity at any particular site has been counted as *one* deformity, regardless of whether it was uni- or bilateral.

Spinal deformities occurred with approximately the same frequency in both men and women, while, in general, those of the extremities were somewhat less common in women (cf. p. 87). There was a marked difference as regards lower leg deformities, these being significantly less

TABLE 24. *Absolute and percentage number of individuals with deformities of different anatomical sites (190 individuals).*

Site of deformities	Males (106)		Females (84)		Both sexes (190)	
	No.	per cent of 106	No.	per cent of 84	No.	per cent of 190
Spine	43	40.6	35	41.7	78	41.1
Humerus	5	4.7	6	7.1	11	5.8
Elbow	24	22.6	10	11.9	34	17.9
Forearm	13	12.3	4	4.8	17	8.9
Hand (and fingers)	7	6.6	1	1.2	8	4.2
Pelvic bones and hip	1	0.9	2	2.4	3	1.6
Femur	27	25.5	17	20.2	44	23.2
Knee	3	2.8	2	2.4	5	2.6
Lower leg	37	34.9	12	14.3	49	25.8
Foot (and toes)	5	4.7	2	2.4	7	3.7

common in women (14.3 % as compared with 34.9 % in men). Deformities of the elbow also appeared to be somewhat less common in women ($P \simeq 0.05$); this is probably related to the fact that elbow fractures are also less common in women than in men. The relationship between fractures and deformities will be further discussed later.

For the sake of completeness, the frequency figures for both sexes combined are given in Table 24. Considering the sex differences discussed above, they are not of great interest. On the basis of these figures, however, it may be generally said that the spinal deformities are definitely the most common (about 40 % of the patients). These are followed by deformities of the femur (20—25 %), the lower leg (about 35 % of the men and 15 % of the women), the elbow (20 % of the men and 10 % of the women), and lower arm deformities in about 12 % of the men and 5 % of the women. Deformities of other bones of the extremities (including the hand and foot together) occur infrequently, and are somewhat more common in men. Upper arm deformities are an exception, as mentioned above, probably being of more frequent occurrence in women (7 % in women and 5 % in men).

10. The relationship between fractures and deformities

The question of a relationship between fractures and deformities may be of interest. The percentage distributions of fractures and deformities in different sites in the extremities have therefore been compared in Table 25. In this connection, bilateral fractures or deformities in corresponding sites have been counted as two separate lesions. The right hand part of Table 25, however, gives the actual numbers and percentage incidence of individuals with deformities at the different sites enumerated, irrespective of whether the deformities were bilateral or not. Fractures and deformities of the spine, ribs, shoulder girdle and pelvis have not been included in this comparison, as, in the first place, the numbers and sites of these fractures are more uncertain, and, secondly, the deformities in these localities are more difficult to assess.

In comparing the percentage distribution of fractures and deformities in the same individuals (73 males and 66 females, for whom the site of all fractures is known), a significant difference is obtained ($P<0.001$). The greatest deviation is found between the percentage figures for fractures and deformities of the elbow (and forearm). The incidence of deformities of the elbow is considerably higher (23.5 ± 3.7 %), and deformities of the forearm lower (7.4 ± 2.3 %) than the corresponding figures for the fractures (8.5 ± 1.0 and 15.2 ± 1.4 % respectively).

TABLE 25. *Comparison between the percentage distribution of fractures and that of deformities in different sites of the extremities.*

Locality	73 males and 66 females (139 ind.)				Deformities of all 190 cases examined	
	Fractures		Deformities			
	No.	%	No.	%	No.	%
Humerus	33	4.7	6	4.4	11	6.3
Elbow	60	8.5	32	23.5	34	19.4
Forearm	108	15.2	10	7.4	17	9.7
Hand (and fingers)	61	8.6	6	4.4	8	4.6
Femur	210	29.6	37	27.2	44	25.1
Knee	30	4.2	4	2.9	5	2.9
Lower leg	171	24.1	37	27.2	49	28.0
Foot (and toes)	36	5.1	4	2.9	7	4.0
Total	709	100	136	100	175	100

Even if it were assumed that a number of highly situated lower arm fractures resulted in deformities which were denoted as those of the elbow, this would still be insufficient to explain the excess of deformities around the elbow over the corresponding fractures. It is probable that fractures occurring around the elbow, especially in the olecranon, are particularly liable to defective healing and therefore result in a high frequency of deformities. Added to this is the fact, as mentioned previously (pages 75 and 84), that very often these fractures pass unobserved; this may mean, partly, that they were not recorded, and, partly, that they healed without proper treatment and therefore ran a greater risk of resulting in a deformity.

The most common fractures in the lower extremities are those of the femur and lower leg. In both these sites the relative number of deformities is approximately the same as that of fractures (25—30 %). In other localities the number of both fractures and deformities is lower, and the excess of the percentage number of fractures over that of deformities is also more marked (about 5—9 % for fractures and 3—5 % for deformities).

The 139 individuals on whom this comparison was based, constitute a selection (see p. 65) of individuals with a relatively smaller number of fractures, being those for whom the site of all fractures was known. It is therefore of interest, that the percentage distribution of deformities in different sites of the extremities in all the 190 cases examined (the entire material) is in very good agreement with the corresponding distribution in the 139 selected cases. Hence, it seems reasonable to suppose that the distributions found in the 139 cases are sufficiently representative of the true picture.

That the greatest relative frequency of deformities occurs in the elbow, lower leg and femur can probably be interpreted as an expression of the fact that these skeletal parts are most subject to trauma and strain, and are also most difficult to keep strain-free during the healing period.

As mentioned previously, the type and manner of occurence of some deformities of the long bones seem to support the concept that these are more likely the result of a plastic deformation than of badly healed fractures. The following shows the frequency of curved femurs in combination with the number of femoral fractures (excluding fractures of the femoral neck). The 139 individuals for whom all fractures could be localized are used as a basis for these figures.

Number of femoral fractures	Number of femurs	of which curved		
		Number		Per cent
No fractures	198	6	=	3
1 fracture	41	1	=	3
2 fractures	17	5	=	3
3 or more fractures	22	15	=	68
	Total 278	27	=	10

Even if the figures are subject to a certain degree of uncertainty (in a few cases there was some uncertainty whether the fractures were left or right sided), it is evident that there is a marked relationship between the number of fractures and the tendency to curvature, or, in other words, that the fragility (measured by the number of fractures) and the tendency to curvature are positively correlated. It may be pointed out that in 6 cases, a curvature of the femur had occurred without previous fracture, and that 7 femurs had sustained at least 2 fractures (2 had 2 fractures, 3 had 3 fractures, and 2 had 4 fractures) without any apparent bending.

The forearm and lower leg, which also showed a large number of fractures, could not be analysed in a similar way, because in several cases information was lacking as to which side had been fractured. In 3 cases, however, (Nos. 130 : 2p and 161 : 6p — bilateral) bending of the forearm, and similarly in 3 cases (Nos. 174 : 1p — bilateral, and 140 : 1p), bending of the lower leg, were manifest without any fracture being previously observed.

In conclusion, it may be said that there is a distinct association between the number of fractures and the number of deformities in different sites. With increased fragility there is thus a subsequent risk of deformity. It does not appear, however, that badly healed fractures are always the only direct cause of deformities.

In some cases deformities appear without foregoing fractures. These may possibly be due to plastic deformation of the defective bone tissue under the combined strain of body weight and muscle tone. It is probable for most deformities that increased bone fragility and plasticity are both contributory factors. Further, increased bone plasticity probably increases the risk of defective healing of fractures, particularly in bones

which are especially subject to the strain of the body weight and muscle tone.

The deformities and the handicap which they cause thus seem to be due to two different conditions in the bone tissue, i. e. increased plasticity and increased fragility. It may be supposed that in osteogenesis imperfecta the basic cause of these conditions is a common defect of the bone tissue, as yet unknown.

E. Slender body build and small stature

The slender body build in osteogenesis imperfecta was probably first described by Axmann (1831), and this feature combined with small stature was later commented on by Harman (1910), Cockayne (1914), Holcomb (1931), Seedorff (1949) and others.

Although there were great variations in body build and height among the 190 individuals investigated, there was nevertheless a general impression that they tended to a certain degree to be short and slender. The question must be raised, however, as to whether the slender body build is not due, at least to some extent, to an inactivity-atrophy, and, more important, whether the small stature is not secondary to deformity.

Table 26 shows the mean height in different handicap groups in all the cases investigated over the age of 16 years, whose body height was measured, regardless of whether or not deformities had been found. Not

TABLE 26. *Mean height of 68 males and 58 females over 16 years of age in different handicap groups.*

Physical handicap	Males		Females	
	No. of ind.	Mean (cm)	No. of ind.	Mean (cm)
None	40	169.4	40	155.3
Slight	16	161.4	10	145.3
Fairly severe	8	142.8	3	133.0
Severe	4	115.0	5	112.0
Fairly severe + Severe	12	133.5	8	119.9
Total	68	161.2	58	148.7

unexpectedly, the body height decreased with an increasing degree of handicap, and in the most severely affected group was on an average less than 120 cm. There is no doubt that this decrease in the body height can be ascribed, at least partly, to deformities of different types.

A more certain estimate of the true body height in these cases, compared with the rest of the population, is probably obtained by including only those cases who exhibited no deformities of the spine or lower extremities, which could reduce the body height, and also by including only cases above 20 years. Of 122 cases over 20 years of age, only 47 satisfied these criteria, and these were among individuals with milder forms of the disease. Table 27 shows the distribution of these individuals according to body height. The mean height for men in this group is about 171 cm, and for women about 156 cm.

It is difficult to find figures to compare with these among individuals not suffering from the disease. No investigations have been published during the last decades on the body height of adults over the age of 20 years in Sweden. Certain data on diabetics, female sanatorium patients and working women, for whom the body height is recorded, has, however, been obtained from the Institute for Medical Genetics in Uppsala. Information on the body height of 20 year old men at the commencement of military service, was also obtained. On the basis of these figures, and taking into consideration the slowly increasing mean

TABLE 27. *Height of patients (20 years and over) without deformities of spine and lower extremities.*

Males			Females		
Height, cm	No.	Per cent	Height, cm	No.	Per cent
< 155	—	—	< 145	2	8.0
155—159	4	18.2	145—149	2	8.0
160—164	2	9.1	150—154	8	32.0
165—169	3	13.6	155—159	6	24.0
170—174	5	22.7	160—164	4	16.0
175—179	5	22.7	165—169	1	4.0
≥ 180	3	13.6	≥ 170	2	8.0
Total	22	100	Total	25	100
Mean height	170.6 ± 1.9 cm			155.8 ± 1.5 cm	

body height, the mean height of men can probably be assessed at 174 cm, and that of women 163 cm at present in Sweden (Lander 1960).

In comparing these figures with those in Table 27, it can be seen that the mean body height of women with a mild form of osteogenesis imperfecta is significantly shorter than that of the rest of the population. There is also a probable, but not certain, decrease in the body height in men.

Of the 25 women, only three were above the assumed mean normal female body height of 163 cm, while 8 men out of 22 were above the 174 cm calculated as the normal male mean. The tallest woman in the investigation was 172 cm, and the tallest man 186 cm.

It may thus be said in conclusion, that individuals with osteogenesis imperfecta are not necessarily of small stature, but that there is a definite tendency to subnormal values in the body height, even in cases without clinically demonstrable deformities.

F. Characteristic dental changes in osteogenesis imperfecta

Bauer (1920) seems to have been the first to observe any special dental changes in osteogenesis imperfecta. He demonstrated changes in the dentine formation, and this has been verified by later authors (Bergersen 1929, Pindborg 1947, Bergman and Engfeldt 1954, *inter alia*). These changes have been called dentinogenesis imperfecta. Similar dental changes are also found alone, without other signs of osteogenesis imperfecta, and are then usually referred to as "hereditary opalescent dentine". This anomaly is also determined by a single dominant gene difference.

The dental changes are often seen as a change in colour, e. g. "greyish-brown", "brown or yellowish", "bernsteinähnlich", "whitish opalescence", and often as a tendency of the enamel to break and peel off. The teeth are often unusually small.

It has been shown that the dental changes are due to an irregular formation of the dentine which originates from the mesoderm, with abnormally arranged collagen fibrils (Bergman and Engfeldt 1954). Cracks in the outer layer of the dentine cause the enamel to break. The

enamel itself, which arises from the ectoderm, is said to be of normal structure.

Apart from these changes, in a number of cases of osteogenesis imperfecta a striking irregularity in the position of the teeth has also been observed, and sometimes a delayed dentition (Pindborg 1947, Seedorff 1949).

No correlation has been found by previous authors between the occurrence of dental changes and the degree of severity of the disease in its other manifestations (Seedorff 1949). In this investigation also, it has been observed that severely handicapped and deformed individuals can have perfect teeth, while those without deformity or handicap can have characteristic dental changes.

All the 190 cases were examined for dental changes. In a number of cases information was obtained that the teeth had decayed early in life. It could not, however, be determined whether the changes were typical of those found in osteogenesis imperfecta, or just ordinary caries. These cases, 41 in number, were therefore excluded from the material. Of the remaining 149 cases, 19 were found to have characteristic changes of colour and enamel, and 8 had pronounced irregularity in the position of the teeth. Table 28 shows the distribution of these cases in different handicap groups.

In the groups "no handicap" and "slight handicap", dental changes were observed in 12 % of the cases (14 individuals out of 120), and in

TABLE 28. *Dental changes in 149 patients with osteogenesis imperfecta with different degree of physical handicap.*

Physical handicap	No. of assessable cases	No. with dental changes			
		Brownish-yellow colour and fractured enamel	Marked irregularity only of teeth	Total No.	No. of changes per cent
None	102	7	4	11	10.8
Slight	18	2	1	3	16.7
Fairly severe	14	4	1	5	35.7
Severe	15	6	2	8	53.3
Total	149	19	8	27	18.1

the groups "fairly severe" and "severe handicap" in 45 % of the cases (13 individuals out of 29). The dental changes in this material are thus significantly more common in individuals for whom the disease gave rise to more severe handicap, than in the other cases ($P<0.001$). No significant differences between the sexes were shown, 17 % of the men and 20 % of the women exhibiting the characteristic dental changes.

G. Hyperlaxibility. Liability to distortions. Pes plano valgus

As early as in 1831, Axmann observed the tendency to articular distortions. Spurway (1896) reported that the cases in the family which he described suffered from "bruises and sprains without number". Seedorff (1949) regards hyperlaxibility, i. e. extensibility and flaccidity in the joints, as a fourth cardinal symptom in osteogenesis imperfecta. Key (1926) is of the opinion that hyperlaxibility is caused by a weakness in the connective tissue of the ligaments and joint capsules, and possibly by a certain degree of muscular hypotonia. Seedorff (1949) believes however that this only partly explains the phenomenon, and points out a defective development of the balls and sockets of the joints as yet another contributory cause. Seedorff observed a high frequency of talipedes calcanei valgi, and ascribed this to the same causes as those of hyperlaxibility.

As shown in Table 8, signs of hyperlaxibility were found in nearly 45 % of our cases, tendency to distortion in nearly 35 %, and pes plano-valgus in 40 %. The liability to distortion occurs more often in women (42.9 %) than in men (28.9 %). No certain difference between the sexes was found as regards hyperlaxibility and pes plano-valgus.

It seems probable that hyperlaxibility, liability to distortion, and even the weak foot build (pes plano-valgus) have all the same basic cause, i. e. a weakness and flaccidity in the ligaments and joint capsules. Joint flaccidity is in itself a very important symptom, and is often a greater disadvantage than the bone fragility itself.

The following are examples of this disadvantage caused by joint flaccidity. A boy (case No. 10:1), 8 years old, had had 6—7 fractures, all of which had healed well without any trouble. He was most disturbed, however, by weakness

of the feet and pronounced flat foot, which hindered his movement and prevented him from taking part in games. Another case (No. 120:1), a young man, by reason of a similar weakness of the feet, commenced training as a motor winder, in which occupation he had to work sitting at a bench. He also had a pronounced hyperlaxibility of the fingers, however, which made it difficult to hold and manipulate the relatively heavy articles used in this work. For this reason he had to consider a change of occupation.

As pointed out by Seedorff (1949), flaccidity of the joints also plays a large indirect role as a cause of sprains or fractures. The joints most often affected by flaccidity are those of the fingers, foot and knee.

H. Blue sclerotics

As previously mentioned, E. Axmann observed blue sclerotics in association with bone fragility as early as in 1831. Since Spurway (1896) and Eddowes (1900) rediscovered the symptom in connection with osteogenesis imperfecta, it has been observed in the majority of the cases of hereditary bone fragility.

All the authors seem to agree that the blue tinge is due to an increased translucency of the sclerae. The chorioid, rich in blood vessels, seems to shine through, giving rise to the blue tinge. Buchanan (1903) is often quoted in this connection. He had the opportunity of examining an eye from a 9 year old girl with blue sclerotics, and found an abnormally thin sclera (only 1/3 of the normal thickness). There is no mention, however, in the report of this case, about other signs of osteogenesis imperfecta, e. g. fractures. Casanova (1934), however, found extremely thin sclerae in a 9 month old girl, who exhibited both bone fragility and blue sclerotics. In one case (an 11 month old child), described by Bronson (1917), Patterson found, on the other hand, "that the sclerotic was of normal thickness, and the size and number of fibres normal for a child of that age". Bronson writes: "Since this infant had the typical blue sclerotic, the more probable theory of its etiology is that of increased translucency rather than decrease in thickness." Voigt (1926) was not able to demonstrate any abnormal decrease in sclerotic thickness, but considered the increased translucency to be due to a qualitative structural change. Follis (1952) and Ruedemann (1953) maintained that they could demonstrate a qualitative difference from the normal sclero-

tics, in the sclera of three cases of osteogenesis imperfecta. They claimed that there was a deficient collagen content and an increased content of immature precollagen fibres, and were of the opinion that the increased scleral transparency was probably due to this lack of collagen. They also found, however, that both the sclerotics and the corneae were thinner than normal.

It was discussed in the section on diagnostic criteria, that there was some divergence of opinion regarding the occurrence of blue sclerotics in osteogenesis imperfecta. While a number of authors, including Holcomb (1931) have described hereditary cases of typical osteogenesis imperfecta, in whom the sclerae were apparently not blue, Seedorff (1949) considered that blue sclerae could always be found by an observer with sufficient experience. It is obvious that such a controversy must be due to differing definitions of blue sclerotics. The definition used in the present investigation has been described on page 16.

As may be seen in Table 8, according to the definition given on page 16, blue sclerotics occurred in 84 % of the surviving cases examined. Information regarding the colour of the sclerotics was received for 10 of the lethal cases, in 8 of whom a striking scleral blueness was reported.

No definite correlation could be demonstrated between the degree of severity of the bone fragility and the intensity of the blueness. Some cases with intensely blue sclerotics had had only mild manifestations of bone fragility, while there were others with severe fragility in whom there was only slight blue colouration.

It is worthy of note, that cases of osteogenesis imperfecta with and without the sign of blue sclerae, do not as a rule occur simultaneously within any one family. In this investigation only one exception to this rule was found. This was in one of the sibships with several cases of the disease but with apparently normal parents (sibship No. 97). This sibship comprised six brothers and sisters, four of whom suffered from bone fragility. Of these four, two had such pronounced blue colouring of the sclerae as to be noted as abnormal. In the other two, the blue shade, according to my assessment, was within normal variations. Seedorff seems to have diagnosed blueness when only the slightest blue shade was evident in the sclerae. In such a case, however, the degree of blueness might not be differentiated from normal variations.

Seedorff (1949), and other authors, are of the opinion that the blue tinge of the sclerae decreases with age. This has also been suggested by

a few patients in the present investigation. However, no definite evidence has been found. In comparing cases in any one family, the blue shade of the sclerae in the older persons did not appear less pronounced than in the younger. It is possible that the blue tone, when observed superficially, may be less conspicuous in older persons because of degenerative conjunctival changes in the region of the rima palpebrarum.

Arcus corneae

As pointed out by Seedorff (1949), arcus senilis has been observed previously in cases of osteogenesis imperfecta by several authors (Peters 1908, van der Hoeve and de Kleyn 1918, Key 1926, *inter alia*). "Arcus senile" or "gerontoxon" refers to the occurrence of a ring-shaped turbidity of the periphery of the cornea (Ask—Berg 1936). A similar phenomenon in the new-born is denoted as embryotoxon. The phenomenon has also been simply denoted as arcus corneae.

In the present investigation the symptom was found in 28.9 % of all the 190 cases examined (men 27.4 % and women 31.0 %). Amongst those below the age of 50 years, arcus corneae was found in 15 % (males 15.1 %, females 14.9 %). Of the 22 lethal cases, a white ring near to the limbus corneae was reported in only one. Such symptoms are, however, seldom noted in the hospital records, even when they are present. Unfortunately, no information has been found concerning the frequency of arcus corneae in individuals not suffering from osteogenesis imperfecta, and therefore no quantitative comparison has been possible. It does seem probable, however, that the symptom is more common in osteogenesis imperfecta than in normal individuals.

J. Some aspects of deafness in osteogenesis imperfecta

As previously mentioned, deafness in association with fragility and blue sclerae was first observed by Adair Dighton (1912), Bronson (1917) and van der Hoeve and de Kleyn (1918). Both Bronson and van der Hoeve stated that the deafness was of the conduction type, in some cases combined with labyrinthine deafness, thus analogous with that found in otosclerosis. Histological examinations have also shown focal

changes of an otosclerotic type in the bone of the labyrinthine capsule, especially in the bone at the front edge of the oval window (Ruttin 1922, Gimplinger 1926). According to several authors, the deafness usually begins, as in otosclerosis, at the age of 20—30 years, but can begin either earlier or later. The course of deafness is generally progressive, but may also be arrested (Jelnes 1949, Seedorff 1949).

Different frequencies in the incidence of hearing impairment have been given by different authors. Bell (1928), in a review of the literature, found that of 162 cases for whom information on hearing was given, 98 suffered from deafness (i. e. 60.5 ± 2.6 %), but that there were 269 cases for whom there was no information regarding hearing. No information on deafness was given for any of the cases in Bell's material, who had bone fragility but not blue sclerotics. Fuss (1935) found the incidence of deafness to be 23.7 %, and Seedorff (1949) reported an incidence of 26 %.

At the interview and examination of the 190 cases, information was also noted regarding hearing, and a rough hearing test was performed. Otoscopy was not carried out. As a rule the hearing examination consisted of testing the hearing with a whispering tone. If the patient heard the whisper from a distance of more than 4 metres, the hearing was denoted as normal. When the whisper was heard from close to the ear and up to, but not over, a distance of 4 metres, the patient was recorded as being slightly deaf. In this group also, two cases were included whose audiograms indicated some impairment, in spite of the fact that they heard whispering from a distance of over 4 metres. The deafness was noted as severe, when the whispering tone could not be heard at all, while a conversational tone was heard, and very severe when neither the conversational nor the whispering tone could be heard. When the hearing defect was greater on one side, the degree of severity was assessed by the more defective ear. Six cases of unilateral deafness were also included.

Twelve cases with impairment of hearing, for whom there was definite or suspicious information regarding a previous otitis, were omitted from the material.

Table 29 shows the occurrence of deafness in the 190 cases investigated, as assessed by the above criteria. As shown in the table, the frequency of hearing defects, with no previous history of otitis, was about 23 % for the whole material. There was no significant difference between the sexes. These frequency values, which seem to be similar to

TABLE 29. *Incidence of deafness in 190 patients of different ages. (Both sexes)*

Age at examination (years)	No. of individ.	No. with deafness				
		Slight	Severe	Very severe	Total No.	Per cent
0— 9	24	—	—	—	—	—
10—19	44	3	—	—	3	6.8
20—29	29	2	—	1	3	10.3
30—39	31	8	2	1	11	35.5
40—49	25	6	1	1	8	32.0
50—59	18	5	3	1	9	50.0
≥ 60	19	2	3	4	9	47.4
Total	190	26	9	8	43	22.6

those reported by Fuss and Seedorff, do not, however, reflect the risk of deafness in osteogenesis imperfecta, since it may be presumed that a number of the children and young people included, who at the time of the investigation exhibited no deafness, would develop it later in life. The table also shows the increase in the frequency of deafness in the older age groups. The frequency in the age groups 30—39 years is especially marked, more than 30 % having impaired hearing. There is a further increase after 50 years, but since in these age classes some physiological decrease in acuteness of hearing can be expected, this increase is less certain.

The age at the first onset of deafness is known in 39 of the 43 individuals. Table 30 shows the distribution of the age at first onset among different 10 yearly periods.

The somewhat rare first occurrence of deafness over the age of 40 years, must be considered with regard to the fact that the number of cases in the higher age groups in the whole material was relatively small. Table 31 (columns 1—4) shows the number of cases based on the age at onset of deafness in relation to the number of years of risk in each age period. The number of individuals with deafness at a certain age, calculated from these figures, is given in the right hand part of the same table. By noting the number of years for which the indi-

TABLES 30. *Age at first onset of deafness, and degree of physical handicap.*

Age at first onset of deafness	Degree of physical handicap				Total	
	None	Slight	Fairly severe	Severe	No.	Per cent
0— 9	2	2	—	1	5	12.8
10—19	2	4	—	—	6	15.4
20—29	4	2	2	—	8	20.5
30—39	8	2	—	—	10	25.6
40—49	6	1	—	—	7	17.9
≥ 50	1	2	—	—	3	7.7
Total	23	13	2	1	39	100

TABLE 31. *Risk of deafness in different age periods and calculated number of cases of osteogenesis imperfecta with deafness at different ages.*

Age period (years)	No. of years of risk in each age period	No. of individuals with deafness	Annual risk of deafness per mille (0/00)	Age (years)	Calculated No. of cases with deafness, per cent
0— 9	1.768	5	2.8	10	3
10—19	1.330	6	4.5	20	7
20—29	952	8	8.4	30	15
30—39	614	10	16.3	40	28
40—49	328	7	21.3	50	42
50—69	161	3	18.6	60	52

viduals had lived within different age intervals, before the onset of deafness, and placing the number of onset cases in relation to the given number of years "under risk", an average annual risk of being affected by deafness is obtained. These risk figures (per mille) are given in column 4 of Table 31. As may be seen, the risk figure increases relatively evenly up to the age of 50 years. Nothing in these figures indicates that the disposition to deafness which accompanies osteogenesis imperfecta is especially marked at any particular age. From these risk figures, it may be estimated that at the age of 40 years about 30 %, and

at 60 years about half of the cases with osteogenesis imperfecta, suffered from deafness (columns 5—6, Table 31). The figures agree satisfactorily with those given in Table 29. No differences between the sexes were apparent.

There was no certain difference as regards the frequency of deafness between the different handicap groups. Of 122 cases without impediment of movement, 25 cases suffered from deafness (25/122 = 20.5 %), and of 68 cases with impediment the corresponding figure was 18 (18/68 = 25 %). It appears therefore that deafness has no direct relationship with the degree of bone fragility. Neither does the deafness, when present, appear to run parallel in severity with the degree of physical impediment. Whether deafness appears relatively earlier in handicapped than in non-handicapped cases, could not be assessed with certainty as the material was too small (cf. Table 30).

Deafness was also found in cases with normally coloured sclerotics. No significant difference was found in the frequencies of deafness in cases with sclerotics of normal colour and cases with blue sclerotics (cf. Table 38).

As regards the course of the deafness, several patients reported that it had become progressively worse since it was first noticed, in some cases quickly, and in others more slowly. Three patients observed a deterioration in hearing associated with pregnancy (compare the discussion on exacerbating factors, page 111 ff.). In Seedorff's material four cases of deafness occurred in association with pregnancy. This is also analogous with the situation sometimes found in other types of otosclerosis.

It is of interest that an improvement in hearing was obtained in two of the patients after a fenestration operation. This was also reported by Jelnes (1949) in one of his cases.

It also may possibly be of interest, that in two of the cases unilateral deafness was reported to occur after injury; in one case following a blow on the ear during school age, and in the other after a skull injury at the age of 21 years. It is thus perhaps possible that the deafness may have been caused by luxations of the auditory bones, as described by Flisberg and Floberg (1960) in skull injuries.

It is evident that severe deafness creates a further disadvantage in addition to the handicap caused by bone fragility. For at least three cases who were not at all, or very little, impeded by their bone fra-

gility, the deafness in itself constituted a severe handicap and forced them to change their occupations.

The data on deafness presented here are not exhaustive. A more exact analysis would require a thorough otological examination of all the cases. This was not considered feasible within the scope of the present investigation. In spite of the incompleteness of the observations it is nevertheless considered of value to report them together with the other observations on the material. Partly, they complete the general picture of the disease, and, partly they may provide a basis for any special investigations which may be carried out later.

K. Tendency to subcutaneous haemorrhage and other types of haemorrhagic diathesis

Several authors have reported signs of different forms of haemorrhagic diatheses in osteogenesis imperfecta. Bauer (1920) and Seedorff (1949) noted an increased liability to subcutaneous haemorrhage without any other hemorrhagic tendencies. Other forms of haemorrhagic diathesis have also been reported. Voorhoeve (1919) found ten cases of hemophilia in the family which he investigated. Blencke (1924), who described two children and their mother, all of whom had blue sclerotics and bone fragility, stated that the mother bled to a great extent when wounded. After a tooth extraction in her youth she lost so much blood that she had to be taken to hospital after a few hours. No haemorrhagic tendencies were, however, observed in the children. Gautier and Guinand-Doniol (1952) described a case of osteogenesis imperfecta in connection with thrombasthenia (Glanzmann type) in a 13½ month old girl; both her parents were found to have an abortive form of thrombasthenia, and both the mother and the maternal grandmother had blue sclerotics. These findings were interpreted as due to the accidental coexistence of two separate genetic factors. Siege, Friedman and Schwartz (1957) described a young man with osteogenesis imperfecta and a haemorrhagic diathesis, who had increased capillary fragility, a prolonged bleeding time and an abnormal prothrombin consumption, all of which were ascribed to defective thrombocytic function. The authors also referred to the case of osteogenesis imperfecta with abnormal thrombocytic func-

tion, described by Gautier and Guinand--Doniol, and stated as "probable (from the similarities between that case and ours) that these two mesenchymal defects are related and not simply coincidental".

In this material, as well, both an increased liability to subcutaneous haemorrhage, and also in several cases other haemorrhagic tendencies, were found.

As regards subcutaneous haemorrhages, the patients often stated spontaneously that they bruised very easily. Frequently they had no knowledge of any trauma, and at other times the bruises were caused by very slight injuries. As may be seen in Table 8, this tendency was noted in 31 % of all the cases investigated (17.9 % in men and 47.6 % in women). In no case was this symptom so severe as to require medical attention. Unfortunately no information has been procured regarding the frequency of subcutaneous haemorrhage in individuals not suffering from osteogenesis imperfecta. It would seem to be a general observation that the phenomenon is not unusual even in healthy individuals. The frequency figure of 31 % among the individuals investigated here, appears though to be high.

From six cases (3 men and 3 women), information was obtained which might indicate another type of haemorrhagic diathesis.

A 67 year old man (case No. 14:7) stated that he usually bled for 10—12 days following a dental extraction. This had been a great problem. On the other hand, he had no excessive bleeding from small cuts, or during operations, and neither was he especially subject to bruising. During hospital care in 1953, the following values were found; bleeding time 1 min. 55 sec., coagulation time 1 min. 15 sec., Quick's index 83 %, thrombocytes 230,000, thus normal values. He was considered to be a hemophiliac.

A 53 year old nephew (case No. 15:1p) of this man had also had prolonged bleeding after dental extractions, and once also after an operation. He was also believed to be a hemophiliac. In 1947 the following values were found: bleeding time 3 min. 30 sec., coagulation time 5 min. 50 sec., thrombocytes 284,000, prothrombin index 30 % and in 1955: bleeding time 4 min. 40 sec., coagulation time 3 min. 55 sec.

A 51 year old woman (case No. 18:Mp) stated that she bled for several days after small cuts, and that she bruised very easily. There was, however, no mention of a haemorrhagic tendency in the hospital records when she had a fenestration operation. Her 26 year old son (18:2p) also stated that he bled for a long time after cutting himself, but did not bruise particularly easily.

A 31 year old woman (case No. 72:M) said that she had had some difficulties

with haemorrhage after operations, and also that she bruised rather easily. A distant relative of this patient also, a 30 year old woman (case No. 67:2p), was considered by doctors to have haemorrhagic tendencies.

The causes of these haemorrhagic tendencies are not known. Bauer considered the liability to bruising to be a result of the same mesenchymal deficiency which he regarded as the cause of the other symptoms in osteogenesis imperfecta. Siegel et al. also ascribed the disturbed thrombocytic function found in their cases to a mesenchymal defect.

The data obtained from the present investigation are too inadequate for any conclusions to be drawn concerning a possible relationship between osteogenesis imperfecta and an abnormal bleeding tendency. A more detailed investigation of the haemorrhagic diathesis in the different cases would of course have been desirable, but was not possible. The problem is nevertheless of great interest, and has often been discussed in connection with this disease.

L. Other signs and symptoms

Several signs and symptoms of disease other than those described so far, were also found more or less sporadically among the cases investigated. Diabetes mellitus was noted, for example, in three of the 190 cases (1.6 %), rheumatoid arthritis in 4 cases (2.1 %), psychiatric conditions in 3 cases (1.6 %), coronary insufficiency in 5 cases (2.6 %), thyroid disorders in 4 cases (2.1 %), bronchial asthma in 2 cases (1 %), peptic ulcer in 2 cases (1 %), and congenital dislocation of the hip in 1 case (0.5 %).

Skin anomalies, which have been described in rare cases by other authors, such as ichthyosis vulgaris (Ries 1951), cutaneous dysplasia (Lehsan 1951), hypertrophic scar formation (Scott and Stiris 1953), Ehlers-Danlos syndrome (Biering and Iversen 1955) and macular atrophy of the skin (Blegvad and Haxthausen 1921, Grimalt and Korting 1957) were not observed in this series, although attention was directed towards any skin defects. In a number of the cases examined the skin appeared to be thinner and more delicate than in other individuals, but this feature was not of general occurrence, and its variations, as far as

could be assessed, could not be said to be more marked than those found in individuals not suffering from the disease. It is possible however that a histological examination, by means of skin biopsy, of all the cases in the investigation, might show definite deviations from the normal (cf. Follis 1952, 1953).

One symptom which, according to Seedorff (1949) is common to all patients with osteogenesis imperfecta, is an asthenia with rapid fatiguing. The same observation was made by a female patient (case No. 80:M) belonging to one of the largest families in this material. She mentioned spontaneously that both she herself and those among her relatives who had blue sclerae, became tired far more quickly, and were more sensitive, than those of her relatives without blue sclerae. This general feeling of tiredness and rapid fatiguing was noted in 10 (= 5.3 %) of the 190 cases examined. It was striking, however, that the majority of these cases, also, were ambitious, and sought in all ways to overcome their handicap.

The different symptoms mentioned above were noted in such a low frequency in the material that they could not, with any degree of certainty, be correlated with osteogenesis imperfecta.

M. Exacerbating factors in osteogenesis imperfecta

In one of the two original cases of this investigation (case No. 10:M), a marked exacerbation of the condition was observed during pregnancy and lactation, with an increase in osteoporosis resulting in vertebral compressions. This patient was described in detail by Berfenstam and Smårs (1956). Seedorff (1949) described four cases in whom an already existing deafness became aggravated during pregnancy. Following these observations, the present investigation was planned so as to attempt to collect evidence of exacerbating factors.

If, as seems correct, osteogenesis imperfecta is due to an osteoporosis or an atrophy of the bone tissue, i. e. a deficient renewal of the bone matrix, exacerbations of the disease should be associated with increased bone atrophy or increased osteoporosis. It is known that bone atrophy can occur normally with inactivity (atrophy of disuse), during the

menopause (postmenopausal osteoporosis), in senility (senile osteoporosis), and as a result of inadequate diet (cf. McLean and Urist 1955). Some cases of osteoporosis occurring in association with pregnancy have been described by Nordin and Roper (1955).

Even if this investigation cannot be said to have produced any definite evidence of the occurrence of exacerbating factors, a few observations which indicate that the disease may be aggravated by a) pregnancy and lactation, b) inactivity and c) inadequate diet, are nevertheless worthy of mention.

A short account of such cases follows:

a) Accentuated symptoms associated with pregnancy and lactation

Spinal symptoms:

1. Case 10:M. First pregnancy at 28 years. Increasing ache in lower part of back during the last 2 months of pregnancy. X-ray examination 1 month post partum showed osteoporosis. The patient breast-fed the child for 6 months. Towards the end of this period the pains in the back became worse and the patient had difficulty in walking. A further X-ray examination at this time showed increased osteoporosis, and recently produced vertebral compressions. About 2—3 months after lactation ceased, a spontaneous improvement began. After a further 2 months, treatment with testosterone was begun, and the improvement continued. At an X-ray examination 6 years later, no definite osteoporosis was seen.

2. Case 37:M. First pregnancy at 34 years. No spinal symptoms during the pregnancy. After the delivery, pains in the back began, and at the same time a curvature of the lower thoracic spine was noticed. The patient breast-fed the child for only a few weeks, as the milk supply was poor.

3. Case 28:M. Spinal symptoms with pains in the back and legs associated with pregnancy and lactation during the 2nd, 3rd and 4th pregnancies (at 21, 24, and 28 years of age). The patient said that as far as she could recall, the symptoms were not relieved until the end of lactation.

4. Case 40:M. Pain and a feeling of weakness in the back post partum at 18 and 20 years of age. Had difficulty in lifting the baby.

5. Case 56:M. Pain in the back at the age of 28 years for one month following the first delivery.

Deafness:

6. Case 1:M. Some months after the first delivery at 35 1/2 years, the patient noticed impaired hearing.

7. Case 87:M. Deafness began after the 4th delivery at 34 years.

8. Case 142:3. Pregnancy at the age of 21 years, which was aborted during

the 3rd month on eugenic grounds. A few months later the patient noticed that her hearing had deteriorated.

The 190 cases who were examined included, apart from the 8 cases described above, a further 21 cases in whom no exacerbation of the disease was noted during pregnancy.

b) Accentuated symptoms associated with inactivity

1. Case 61:2. A man, who at the age of 49 years sustained a femoral fracture, which necessitated confinement to bed with traction applied to the leg for four months. When he began to be ambulant, he was unable to stand up straight, his back having become contracted and curved. According to the patient himself, his back had always previously been straight.

2. Case 1:M. A woman, who had had only three fractures before the age of 66 years. At that age she sustained first a lower leg and then a femoral fracture, which necessitated immobilization for a long period. The fractures healed well, but during the subsequent months she kept fairly still. During this period she had increasing pains in the back. X-ray examination showed osteoporosis of the spine, and vertebral compressions. This case is possibly an example both of atrophy of the bone tissue due to inactivity, and of senile osteoporosis.

3. Case 86:1. A boy, who possibly had had an unobserved fracture before the age of 1 year. He started to walk at 11 months, but when "his legs would not carry him" he reverted to creeping for a time before he began to walk again. He subsequently played just as other children until he was 7 years old, when he had a severe attack of measles. When he got up again after this one day his right leg bent under him (when he was on the way to the bathroom), and a femoral fracture was confirmed. This healed well, but two years later he sustained first one and then another fracture of the same femur. These were followed by annual fractures of different extremities. It is conceivable, that the first fracture was provoked by an atrophy of disuse caused by recumbency during measles. It is also possible that the measles itself exerted some effect. The following of one fracture by a whole series, as in this case, may possibly be due to the fact that an atrophy of inactivity subsequent to one fracture, increases the liability to further fractures. This might explain, at least partly, why the fractures often occur periodically.

4. Case 159:4. A woman, who in childhood appeared quite healthy until the age of 4 years, when she had measles and whooping cough. When she got up after these illnesses, she sustained her first fracture, and subsequently one fracture followed another (altogether 125 fractures up to the age of 23 years), resulting in severe deformities (cf. the previous case).

5. Case 71:2. A man, who up to the age of 8 years had only had one fracture and had been fully mobile. At 8 years he was knocked down by a motor cycle and sustained several fractures. During his stay in hospital, one fracture followed another, which necessitated remaining in hospital for 2 years.

c) Observations relating to inadequate diet in connection with exacerbations of osteogenesis imperfecta

1. Case 14:9. A woman, who before the age of 34 years had had only one fracture and had been fully mobile. At this age she suffered from increasing pain and weakness in the back, and, subsequently, she also sustained repeated fractures. The patient stated that at this time she had kept to a certain diet for a prolonged period, and had avoided milk and milk foods, which did not suit her. At the same time, pernicious anemia was discovered.

2. Case 51:1. A man, who sustained his first fracture at 1 1/2 years, and subsequently had repeated fractures up to the age of 10 years. The parents stated that he had been particularly difficult as regards food from 1 year to about 10 years of age.

This observation, that a period of fractures had coincided approximately with a period of poor appetite, was made by several parents. It is, of course, far from certain that the poor appetite with consequent poor nourishment contributed in these cases to the fracture liability, even if it could be a contributory cause. The poor appetite might, on the contrary, be caused by the presence of a fracture, or, both phenomena may have a common cause.

3. Case 94:6. A woman who had had repeated fractures since the age of 1 year. From the age of 13—15 years there was a period of increased tendency to fractures, which she herself ascribed to the poor diet during the war years 1914—1918.

To summarize, one may venture to suggest, supported by these briefly reported cases, that an exacerbation of the bone fragility (and of the basic osteoporotic condition) can apparently be produced during pregnancy and lactation, in association with inactivity and infectious diseases, and also possibly in connection with deficient nourishment. It should be pointed out, however, that a deterioration is not by any means general during pregnancy and lactation. The observations made nevertheless give cause for increased vigilance at this time; for example, the carrying of heavy weights, and excessive physical work should be avoided during pregnancy. At the same time the patient should guard against inactivity.

In conditions which enforce immobilization, this should be made as short as possible. Special precautions should be taken to avoid infectious diseases. A complete and satisfactory diet should always be aimed at with these patients. With evidence of accentuated osteoporosis, hormone therapy may be considered. Various forms of orthopedic support are, of course, of great value in many cases.

N. Course of the disease, and the possibilities of influencing it

In the previous sections, each symptom of the disease picture in osteogenesis imperfecta has been described, in so far as they could be illustrated from the material collected. Although in these sections the actual course of the disease has already been discussed in part, a précis will be given here for the sake of continuity. A recapitulation will be made as regards any possible prophylaxis and therapy.

All degrees of severity of the disease may occur. The disease may be so severe as to be fatal; or on the other hand there may be only insignificant symptoms, such as blue sclerotics alone, with few or no fractures.

Lethal cases. In the most severe cases, death occurs at the foetal stage, though some may live up to several months after birth. During the survival period, one fracture follows another, often without any cause other than the movements of the child in its bed, or the handling of the child during its daily care. The skeleton is sometimes extremely weak, and bends or breaks even at the slightest touch. The skull may feel as soft as a balloon filled with fluid, sometimes with interspersed bone islets. The joints are often soft and flexible, lacking all stability. Repeated fractures may result in grotesque deformities of the extremities. The child usually dies of some intercurrent infection. In the extremely severe cases it is usually evident from the beginning that there is no possibility of saving the child, but since transitions to survivable forms do occur, it is desirable in these cases to do one's utmost to counteract deformities.

Surviving cases. While in all the lethal cases, due to its short duration, the course of the disease is rather similar, in the surviving cases large variations occur. It is not possible to draw a distinct borderline between lethal and surviving cases. Severe cases with multiple fractures, ossification disturbances and deformities from birth, whose prognosis appears at first to be almost hopeless, may occasionally survive. The fractures may certainly continue to occur year after year, but with time they usually become less frequent. Pronounced deformities of the extremities, back, thorax, pelvis and head may develop and become permanent.

In other cases the fractures first occur when the child has begun to

walk, or later during childhood, and in some cases not until adult years are reached. It is peculiar, that cases who have shown no signs of bone fragility up to the age of 5—12 years, can at this time sustain their first fracture, followed by a severe period with repeated fractures and deformities. It is difficult to conceive the mechanism responsible for this phenomenon. In a number of cases factors which may produce or exacerbate the disease can be found, while in other cases such factors are apparently lacking. Thus pregnancy and lactation, inactivity, infectious or toxic conditions, and diet deficiencies have been mentioned as conceivable exacerbating factors. Other possible factors may be the endocrinal changes which occur at puberty, at the menopause and in senility, factors which are known to normally influence the building up of the organic matrix of the bone tissue. It must, however, be said that in general the course of the disease appears to be determined by factors, which are as yet completely unknown.

It does however seem possible to affect the final outcome as regards deformities and function. This is illustrated to a certain degree by two cases in this investigation, both men of 27—28 years, who had had over 50 fractures. One of them (case No. 30:F) stated that in spite of his repeated fractures, each one was treated with great care, and he was considered as being only slightly impeded in his movement. The other man (case No. 170:1) also reported that his fractures healed well, as long as they were treated carefully. He stated, however, that his deformities did not develop seriously until it was considered by the doctors that there was nothing to gain by treating the repeated fractures carefully, and treatment was discontinued. This patient had severe impediment of movement (a wheel chair case), but was himself of the opinion that he could have been able to walk if more perseverance had been shown in the treatment of his fractures. It is quite likely that the different outcome of these two cases was not only, and perhaps not at all, due to the different treatment of the fractures, but to other, unknown factors such as modifying genes or other internal and external influences, which are the cause of the frequent periodic deteriorations. It is, however, probable that the fracture treatment is of great significance to the outcome of the course of the disease.

In treating the fractures in osteogenesis imperfecta, the most important point is probably the risk of atrophy of the bone tissue due to inactivity during immobilization.

Apart from the specific fracture treatment, orthopedic treatment is also of great importance. Not least does this apply to the supportive and corrective therapy directed towards the flaccid joints and weakness in the foot ligaments.

Since the bone tissue appears to become stabilized, and the tendency to fractures to decrease after puberty, it is particularly important that these patients receive correct treatment with supporting and correcting measures, when necessary, up to this time, in order to prevent deformities. This also applies, of course, to exacerbating periods at other ages.

As with the bone fragility, the hyperlaxibility also seems to decrease with increasing age. There is no certain evidence that the blue colour of the sclerae decreases with age.

In contrast to several other symptoms in osteogenesis imperfecta, the deafness, as with otosclerosis, is, as expected, progressive. It is also common that the spine contracts more with increasing age, the patient becoming shorter and more bent. This is probably to be ascribed to a senile osteoporosis, which is more pronounced in individuals with osteogenesis imperfecta than in others. Only in exceptional cases do any significant deformities occur in the extremities after the age of 15—20 years.

Regarding osteogenesis imperfecta patients in general, as they appear in an assessment of the 190 cases in this series, it is worthy of note that the majority had no (64 %) or only slight (17 %) impediment to movement, and that only 19 % had a more pronounced impediment to movement. This disagrees to a certain extent with previous opinions. Ostheimer (1914), for example, states "that over one half of all patients remain badly crippled as a result of recurring fractures", and this statement was quoted by Holcomb (1931). Intellectually, the patients seem to be on the whole well equipped. As may be seen in the report of the socio- medical study of the material, they are also well adapted to community life.

As will be shown in the genetic study (see p. 160 ff.) the mortality rate does not seem to be increased in osteogenesis imperfecta for those individuals who survive for more than two years.

VIII. Biochemistry, roentgenology, histopathology and pathogenesis. A short survey of the literature

A. Blood chemistry and other laboratory data

Numerous investigations of the blood chemistry have been made in osteogenesis imperfecta. The studies have been concerned mainly with the calcium, phosphorus and phosphatases in the serum. The literature has been reviewed in detail by both Seedorff (1949) and Caniggia et al. (1958).

For calcium and phosphorus, both high and low values have been reported, but in general normal values have been found. Except for a few cases with raised values, the alkaline phosphatase activity has been found to be within normal limits.

Among the cases investigated here, serum calcium values were available for 48 cases, and serum phosphate values for 29. The majority of these showed normal values. In a few cases slightly raised or lowered values were obtained, but as these were only single determinations, they cannot be regarded as significant.

Data on the alkaline phosphatase activity was available for 22 cases. Of these, three cases had raised values, which, however, in one case could be ascribed to the healing of a fracture, in another to an acute cholecystitis, and in the third to hemolysis in the test. Normal values were found for the other 19 cases.

Gebala (1956) found in 8 individuals, consisting of 3 adults and 5 children distributed into three families, raised serum acid phosphatase values. However, in 6 cases in our series, for whom serum acid phosphatase determinations were made, normal values were found.

Previous authors have not reported any pathological values for other blood chemistry determinations. The total protein estimation in 9 cases in the present material, and the serum citric acid estimated in 3 cases, showed no apparent deviations from normal.

No special morphological changes in the blood were observed in this material.

Several authors cited by A. E. Hansen (1934, 1935) found the total quantity of ash to be decreased to 33—34 weight % compared with 60—66 % for normal bone. Hansen, in an examination of the mineral balance in two cases of osteogenesis imperfecta, stated that he was able to verify previous informa-

tion on a deficient retention of calcium and phosphorus (and possibly also magnesium), which he considered to be one of the characteristic aberrations in osteogenesis imperfecta.

No detailed studies of the calcium and phosphorus balance were made on this material. In 10 cases the 24-hourly quantity of calcium, and in 6 cases the 24-hourly quantity of phosphate in the urine had been estimated. No deviations from normal values were found.

A. E. Hansen (1934) examined one case post mortem and found "an almost complete absence of phosphatase in the periosteum and sub-periosteal structures, where it is normally abundant".

In conclusion it may be stated, that up to the present time it has not been possible to find, by biochemical methods, any disturbance which throws light on the nature of the disease. From the diagnostic point of view, it is of value to recall that, in general, the blood chemistry in osteogenesis imperfecta has normal values, in contrast to several other skeletal diseases.

B. Roentgenological characteristics

No systematic roentgenological examination was made on this material, which therefore cannot be used as a basis for any general assessment of the X-ray picture in osteogenesis imperfecta. As a complement to the clinical description of the disease, however, a review of the most important X-ray findings as described in the literature is given below.

General structural changes

Practically all authors stress the osteoporotic picture with a lowered calcium density as a characteristic feature. In this connection a more or less high degree of hypostosis, with a thin porotic cortex, enlarged medullary cavity, and sparse trabeculae, has been described (Vorhoeve 1918, Seedorff 1949, Brailsford 1953, Caffey 1956, Hellner und Poppe 1956, Canaggia et al. 1958, *inter alia*). A number of these authors mention, however, that in mild cases, significant roentgenological changes have been sought for in vain. As pointed out by Caniggia et al. (1958), there is always much uncertainty in the estimation of the calcium density unless the more exact densitometric methods are used. Up to the present time it has been considered that the bone must lose 25—30 % of its mineral salts before any change is noticeable with certainty in an X-ray picture (cf. McLean and Urist, 1955, p. 153).

In the long bones, transverse lines opaque to X-rays are frequently observed. Sometimes these are regular and in certain cases symmetrical, when they have been interpreted as pseudofractures (Looser's zones) (Bickel et al. 1943) or enchondral ossification disturbances (Caniggia et al. 1958). In other cases they are more or less irregular, when they have often been interpreted as the

remains of old fractures (Zander 1940, Caniggia et al. 1958). Denser patches in the long bones have also been interpreted as the remains of old fractures. On the other hand, according to several authors, the fractures often leave behind no residual roentgenological signs (Seedorff 1949, Caniggia et al. 1958). Caniggia et al. also mention cystoid formations surrounded by a sclerotic border, which may be found in different parts of the skeleton.

Local roentgenological findings

The cranial bones. Caffey says: "The calvarium may at birth, in severe cases, consist of only a membranous bag with a few small isolated ossification centers. If the patient survives, numerous ossification centers appear with increasing age and the membranous areas are slowly filled in with bone. This gives rise to many wormian bones separated by radiolucent strips of connective tissue which produce a mosaic rarefaction of the vault." This picture was also found in one of the milder cases in the present material (No. 10:1p), who was followed up from birth. It is quite possible that the picture described by Caffey would be found in many of the milder cases, if they were examined early enough. Caffey states "later in infancy and childhood the sutures are usually of normal width and the fontanels are not enlarged", but he also says that "the mosaic rarefaction in the parietal and occipital bones may persist throughout childhood". Caffey states that in his experience the picture he describes is only found in two diseases, osteogenesis imperfecta and cleidiocranial dysostosis.

It has been pointed out by several authors, as a frequently observed roentgenological finding both in younger and older cases, that the parietal bone is flattened ventrodorsally, and that the temporal bones bulge outwards. Occasionally a depression of the base of the skull (platybasia) can also be observed. The cranial bones are usually described as being thin. However, cases with diffuse thickening of the parietal bone have also been reported (Keats, 1957). In many cases significant roentgenological changes in the skull are completely lacking.

Vertebrae. In the many cases with different types of spinal deformities, e. g. kyphosis or scoliosis of different degrees, the X-ray picture shows as a rule compression deformities of the vertebrae (platyspondylisis). The vertebrae often have the biconcave shape typical in osteoporosis (fish vertebrae formation). One case in this material (No. 170:1p), with a pronounced platyspondylisis, has been previously described from a roentgenological aspect by Zander (1940).

Thorax and pelvis. Apart from the thoracic changes secondary to the spinal deformities, Seedorff also states that the thorax can have in this disease, as in cleidiocranial dysostosis, "a peculiar 'bell-shaped'" appearance. Deformities and constrictions of the pelvic bones have been described as being of the same type as in rickets and osteomalacia, but in general these pelvic

changes are only found in cases severely deformed in other respects.

The long bones. These bones, when not deformed, have been described by several authors as appearing characteristically "gracile and slender with a thin porotic cortex and a relatively large medullary cavity". The deformities may be curved or angular, obviously the result of defectively healed fractures. In other cases bending may be observed without any signs of previous fracture, appearing to be due rather to an increased plasticity of the bone, but which could also be the result of repeated subclinical infractions (compare the description of the deformities observed clinically (pp. 83—84). As mentioned previously, a few cases of osteogenesis imperfecta with tumorous swellings of the bone which were possibly secondary to fractures, and which were sometimes difficult to differentiate from sarcoma, have been described. One such case is included in the present material (No. 150:2p). This has been described in detail by Hessén (1952).

C. Histopathology and pathogenesis

Histogenesis and histopathology

No histopathological investigations were made on this material. A short review of the relevant literature follows.

The skeleton of the new-born human normally consists of woven bone, and that of the adult of lamellar bone. The change to lamellar bone takes place during childhood.

In osteogenesis imperfecta a defect seems to exist both as regards the embryonic formation of woven bone and the later reconstruction to lamellar bone.

The development of the skeleton up to the ossification stage seems to take place normally (Looser 1906, Lovett and Nichols 1906, Knaggs 1924, *inter alia*). Subsequently, however, a defective ossification occurs both in cartilage bones and membrane bones. This ossification disturbance, which may be of varying degrees of intensity, is considered to be due to a dysfunction of the osteoblasts (cf. pathogenesis, below). The endochondral ossification no longer takes place, as normally, by a breaking down of the cartilage cells and the apposition of bone tissue to the calcified intercellular matrix by the osteoblasts, but rather there is a direct calcification of the cartilage tissue (Lovett and Nichols 1906, Knaggs 1924, *inter alia*). Even in periostal ossification, there is no normal osteoblastic activity. According to Knaggs and Klotz, instead of the normal differentiation of the osteoblasts from the inner layer of the periosteum, cartilage-like cells are developed, and these are then calcified directly, together with the more or less sparse intercellular substance. Knaggs also describes a similar kind of disturbance in intramembranous ossification. "In a section cut from a part of the calvarium he found larger than normal bone-

cells, which would have been regarded as cartilage cells in any but a membrane bone".

The reconstruction to secondary, lamellar bone, is also defective. Engfeldt et al. found "that this rebuilding was almost or completely absent, indicating a disturbed function of the osteoblasts and osteoclasts".

The result of this disturbed bone formation is an inferior and more or less irregular bone tissue, in which the Haversian systems, so important for tenacity, are completely or partly missing. The basic lamellae of the compact bone, and the trabeculae of the spongy bone are also defectively developed. This immature, irregular formation seems to explain to a great part the fragility in osteogenesis imperfecta.

Osteogenesis imperfecta does not appear to result in any real shortness of stature, the mean body height, disregarding shortness caused by deformities, being only a little less than the normal mean value (cf. pp. 96—98). This fact would seem to be related with the finding that cartilage formation in the epiphyseal plates of the long bones is, as a rule, unaffected, and can provide for a normal growth. The increase in thickness of the long bones is impeded however to a certain extent because of incomplete formation of new bone from the periosteum. This is considered the reason for the slender build and thin cortex which are often seen in the long bones.

Pathogenesis

Biochemically, bone tissue is composed of organic and inorganic fractions. The organic fraction, which in compact bone constitutes about 35 % of the dry, fat-free weight, consists to only a lesser extent of cells, the greater part being the bone matrix. This consists mainly of collagen fibrils, together with a smaller fraction (only a few per cent) of an amorphous ground substance, which together with a small quantity of tissue fluid fills out the space between the fibrils. The amorphous ground substance seems to be mainly of a mucopolysaccharide nature, containing chondroitine sulphate and hyaluronic acid.

The inorganic fraction of the bone, the bone salt, which impregnates the matrix and gives the bone its hard consistency, is composed of calcium, phosphorus, carbon dioxide, citrate and water, together with small quantities of sodium, magnesium, potassium, chlorine and fluorine. The bone salt appears mainly in the form of apatite.

It is held by most authors that it is the bone matrix which is incompletely developed in osteogenesis imperfecta.

The deficient retention of calcium and phosphorus can probably be ascribed to the defective matrix, which is also probably responsible for the osteoporotic picture, which may appear roentgenologically. As in other forms of osteoporosis, an increased retention of calcium has been obtained in some cases of osteogenesis imperfecta after the administration of androgenic and oestrogenic hormones, and it has also been considered that a clinical improvement has been produced by this therapy (Ropes et al. 1946, Hernberg 1952). Albright et al.

(1953) obtained similar results in experiments with serum albumin administered parentally to four patients with osteoporosis, one of whom had osteogenesis imperfecta. A marked calcium retention was observed as long as the supply of serum albumin was continued, and this was presumed to indicate an increased bone formation, produced by the serum albumin which supplied the building material for the bone matrix. After the administration of the serum albumin ceased, however, the calcium balance gradually became negative again. It may be noted in this connection, that with the administration of parathyroid extract, as after large doses of viosterol, Hansen (1935) found an accentuation of the negative mineral balance, especially for calcium and phosphorus, and he therefore cautions against the use of such therapy.

Several authors have concluded, that the deficient matrix formation is due to some defect of the osteoblasts, which histologically appear abnormal (Looser 1906, Bauer 1920, Jeckeln 1931, Wilton 1932, Follis 1952, Engfeldt—Engström—Zetterström 1954, *inter alia*). Bauer maintained that there were also changes in the fibroblasts, odontoblasts and chondroblasts. It is supposed that the osteoblasts form both the collagen fibrils and the ground substance of the matrix, but the mechanism of this is unknown.

It is doubtful in this disease whether it is the collagen fibrils or the ground substance of the matrix which are abnormally organized, or if it is both components. Engfeldt et al. (1954), using polarized light and microradiography, found the following: "In osteogenesis imperfecta the compact bone has a quite abnormal distribution of mineral salts and arrangement of organic fibres". "Instead of concentric layers of collagen fibres (as normally seen) there is a quite irregular arrangement". "The immature fibrillar bone normally seen in the foetus and the newborn infant resembles in several ways the tissue found in osteogenesis imperfecta. Normally this primary bone tissue is rapidly replaced by secondary bone after birth, but in osteogenesis imperfecta this secondary bone tissue is not found".

Follis (1952) maintained that he could demonstrate, by histochemical methods, that the fibrillar tissue both in the skin and in the sclerotics and cornea, and possibly also in the bone tissue, from a case of osteogenesis imperfecta, did not consist of mature collagen, but was similar to the precursor of collagen, reticulin. It is of interest that Follis, like Wilton (1932) pointed out the striking similarity to the histological picture in scurvy. It is known that Vitamin C is necessary for the formation of collagen.

No convincing evidence has been found for the view that osteogenesis imperfecta might be caused by hormonal disturbances.

If the data and views mentioned above are considered together with the genetics of the disease, certain points regarding the etiology and the pathogenesis of the disease emerge. From a clinical and genetic point of view, it has been found that osteogenesis imperfecta is as a rule a genetic disease with simple autosomal dominance exhibiting full penetrance. The disease is thus the result of a gene mutation. There is some basis for the idea that this mutation affects a mechanism which is associated with the building up of the bone

matrix. It is possibly the collagen formation which is particularly affected, not only in the bone matrix but also in other tissues, e. g. the sclerotics, cornea and skin. This concept agrees closely with the hypothesis of Bauer (1940) of "ein patologisch mutiertes Gen, dem normalerweise ein Gen mit der Aufgabe zur Bildung der normalen Grundsubstanzbildung der Stützgewebe entspricht".

According to Beadle (1945) it seems possible that the formation of the protein molecules is controlled by genes, in such a way that each enzyme and enzyme reaction corresponds to a particular gene, "the one gene — one enzyme hypothesis". A number of genes (or parts of genes) are in actual fact considered to be enzymes or their precursors. In consideration of this hypothesis, and the fact that osteogenesis imperfecta is a genetic diesease, which seems to consist essentially of a defective collagen formation, it would seem quite feasible that one of the amino acids essential for the quality of the collagen could, through a mutation, become more or less defective, and in this way give rise to the disease picture. It is, of course, also possible that a defect might instead be found in the ground substance of the matrix.

IX. Genetic and Epidemiological aspects of the disease

A. Genetic problems in osteogenesis imperfecta

1. Problems from previous literature

There has been some divergence of opinion regarding the mode of inheritance in osteogenesis imperfecta. Most authors believe in a simple dominant, autosomal inheritance, e. g. Davenport and Conard (1915), Bronson (1917) and Apert (1928). Of later authors, Seedorff (1949) particularly, has maintained, on the basis of his own large material, that osteogenesis imperfecta is without exception inherited in this way. He considered that solitary cases, whether of the tardive or congenital (lethal) type, were genetically identical with hereditary cases, and were to be regarded as due to new mutations. Seedorff postulated a genetic factor composed of several closely connected genes, viz. one gene for "blue sclerotics", three for osseous fragility and a third, somewhat less firmly linked, gene for deafness. According to this hypothesis, only one of the three genes is affected in the mild form of bone fragility, and in the more severe forms two or three. Seedorff concedes, however, that there need not necessarily be three genes to explain the varying degrees of osseous fragility, if the occurrence of modifying genes is assumed.

McKusick (1956 and 1960), and Caniggia et al. (1958) also agree with the concept of a simple dominant, autosomal heredity, and reject Seedorff's theory that several genes are the basic cause of the different manifestations of the disease, which they ascribe instead to the pleiotropic effect of a single gene.

The theory of a dominant, autosomal heredity in osteogenesis imperfecta is, without doubt, in accord with the majority of the reported cases and families with the disease. Some deviations from this regular heredity have, however, been observed by several authors.

As mentioned previously, Bell (1928), in her review, thus found it necessary to divide the extensive material into two groups. In the larger group, in which one parent had both osseous fragility and blue sclerotics, she found, in agreement with the concept of a simple dominant, autosomal heredity, that 50 % of the children were affected by the disease, and that the disease was transmitted just as often through the father as through the mother. In the other group, with osseous fragility, but where there was no information regarding blue sclerotics, she found a) a higher frequency of men (68.8 ± 3.2 %), and b) that in this group there were no cases reported with a tendency to dislocations, or deafness. She therefore considered that these two groups could not be regarded as genetically homogeneous.

Fuss (1935), in his review of 89 families with altogether 515 cases of hereditary osteopsathyrosis, found that there was nearly always simple dominant inheritance, and that apparent exceptions could probably be ascribed to varying degrees of manifestation. He stressed, however, that cases of osseous fragility also exist, in combination with blue sclerotics, for whom heredity could not be demonstrated. Fuss left open the question as to how these cases should be interpreted.

Some authors have concluded that there is a certain sex predominance, or that transmission is mainly by females (Stiasny 1935). Hirschman (1935), however, thought that in certain families the males were the transmitters. Seedorff seems to consider that the female predominates among the lethal (so-called congenital) cases. Of his seven congenital cases six were girls and one a boy. He also quotes H. Nielsen (1942), who states "that the boy to girl ratio is as 1 to 4". Seedorff however leaves the question open as to "whether this is due to chance coincidence or is genotypically determined". Among the surviving, so-called tardive cases, Seedorff found an even sex distribution.

Several cases have been reported where the disease has missed a generation, i. e. cases where apparently healthy individuals have conveyed the disease from one of their parents to their children. Even if the accuracy of the investigations must on occasion be open to question, such cases do, however, seem to exist. Herndon (1956) described one carefully investigated woman with no signs of osteogenesis imperfecta, whose three siblings and a daughter exhibited unequivocal signs of osteogenesis imperfecta in the form of blue sclerae and bone fragility.

In summary, the following conclusions emerge:

In the majority of pedigrees with osteogenesis imperfecta, the disease syndrome follows a typically dominant, autosomal heredity pattern. Observations have been made, however, which deviate from that expected with this type of inheritance. These differences are as follows:

1. Cases where the disease seems to have missed a generation. Those cases, where several siblings are affected by the disease in spite of the fact that it cannot be demonstrated in the parents, are probably also examples of this phenomenon.

2. Deviations from the expected sex distribution (1 : 1), among a) all those affected by the disease, and b) the affected parents. This would apply especially to the disease group which exhibits osseous fragility but not blue sclerotics.

3. The occurrence of sporadic cases, i. e. cases in whose families osteogenesis imperfecta cannot be demonstrated either in the parents or the other siblings.

These deviations from a regular dominant, autosomal mode of inheritance raise the question as to whether osteogenesis imperfecta is actually a genetically homogeneous disease.

If this were not the case, in only certain cases would the disease be due to a single, dominant, autosomal gene; in other cases there would be a recessive or sex linked gene. Another possibility would be that a number of cases would be phenocopies, i. e. that non-genetic factors during foetal development would give rise to a disease picture, identical with the hereditary disease.

These deviations from the strictly dominant inheritance, however, need by no means always signify another hereditary mechanism. There may also be reduced penetrance. Penetrance is defined as the frequency with which a specific gene is manifested among all individuals who possess the requisite gene. The concept of penetrance is thus distinct from the concept of expressivity, which represents the degree to which a gene is manifested in each individual case.

2. Aims of the genetic and epidemiological analysis of the present material

The present material will be analyzed from the following aspects:

1. Evidence on the penetrance of the gene responsible for osteogenesis imperfecta (provided by the familial cases).
2. Sex distribution,
   a) in the whole material, and
   b) among the parents with osteogenesis imperfecta who had transmitted the disease to their children.
3. The occurrence of the disease among children of sporadic cases.
4. The effect of maternal age and birth rank on the distribution of sporadic cases.
5. Variations in the disease picture between different cases and different families, which could support the concept of a genetic diversity.
6. Interfamilial and intrafamilial variability.
7. The geographic distribution of osteogenesis imperfecta in Sweden.
8. Factors possibly influencing the occurrence of mutation.
9. Mortality.
10. Relative fertility.
11. Mutation rate.
12. Finally there is a short discussion of a linkage-study which was carried out on the material.

For the genetic analysis, the material was divided into two main groups, viz.:

1. Familial cases and
2. Sporadic cases.

The term "familial case" refers to a case, one of whose parents exhibits evidence of the disease. Also those cases are said to be familial, who have one or more affected siblings, although their parents appear unaffected. This may be interpreted either as recessive inheritance or as dominant inheritance with reduced penetrance of the gene in the parental generation.

A case is described as "sporadic" if the previous generations and all the brothers and sisters are unaffected. Of the 266 cases of Swedish birth, in this series, 72 are denoted as sporadic. For all these 72 cases, information was obtained either from the patients themselves, their

parents, brothers or sisters, or hospital records, to the effect that it could be considered certain that symptoms of osteogenesis imperfecta had not occurred in the previous generations or in their brothers or sisters. For 47 of them both parents were examined, for 13 cases, one of the parents, for 9 cases, neither of the parents but the brothers and sisters were examined, and for only 3 cases neither parents nor brothers and sisters were examined.

B. The genetic interpretation of familial cases

The familial cases are classified into three groups:

1. A large group, in which bone fragility and blue sclerotics occur together and in more than one generation,
2. A smaller group in which bone fragility occurs without blue sclerotics and in more than one generation, and
3. A smaller group in which the disease occurs in several brothers and sisters but not in either of the parents.

1. Familial cases with bone fragility associated with blue sclerotics in more than one generation

a) *Penetrance.* An assessment of the penetrance of the gene which is responsible for the disease may be made either directly, or indirectly.

Direct evidence of failure in gene expression is said to be present, when apparently normal individuals, who are offspring of a person suffering from the disease, themselves have children with the disease. It is, of course, necessary that such an assessment be supported by careful investigation.

This material includes 13 chains of three generations, which were examined personally. In none of these was there any evidence of the disease having missed a generation. Neither was there any reason to suggest, in other family chains of three generations (70 chains in all), for whom first hand information was lacking, that the disease missed a generation.

One family (No. 34) was possibly doubtful. The proband, a 14 year old boy, had had 12 fractures caused by inadequate trauma, and blue-

ness of the sclerae was obvious. The maternal grandmother and a maternal aunt (both dead), were stated to have both had very blue sclerotics, and one maternal aunt (who was examined) had markedly blue sclerotics, but as far as was known, none of these relatives had sustained fractures. The mother of the proband (No. 34: M) had had no fractures, deafness, or any definite hyperlaxibility, but her sclerotics had a blue tinge, which both she herself and the rest of the family had noted. The blue colouring was, however, obviously less pronounced than that of her sister and son, and was regarded as pathological with some hesitance. This case is an example of the way in which the expressivity of the gene or genes which are responsible for osteogenesis imperfecta *can* vary greatly.

The fact that no chain of "affected — normal — affected" was observed in our series of cases is, of course, no proof that the gene always has full penetrance.

The gene penetrance may be investigated indirectly, by estimating the ratio of "affected" and "healthy" in all the sibships of the material investigated. With full penetrance, i. e. complete dominance, this should be 1 : 1.

This ratio may be determined according to different methods, which correct against the selection effects produced by the collection of the material through probands. This material collected cannot be considered as complete (see page 33 ff.). The degree of completeness is probably, however, such that a calculation according to the a priori method of Apert-Bernstein, or the sibling method of Weinberg (cf. Schulz, 1936), is valid, although both these methods require a complete material.

For the analysis, no sibships were included with osteogenesis imperfecta cases with white sclerotics, nor those whose parents showed no evidence of the disease. Furthermore, the sibships include only those siblings on whom reliable information was available; e. g., any siblings who had died before the age of 2 years were omitted. The number of such cases with uncertain information was 17 (in 12 sibships).

In Table 32 a survey is given of those sibships included in the material, in which there were cases with blue sclerotics combined with bone fragility.

An analysis by the method of Apert-Bernstein gives the following figures:

No. of sibships	No. of siblings	No. of cases of osteog. imperf.	Estimated No. of cases with osteogenesis imperfecta according to Apert-Bernstein's method with	
			recessive heredity	dominant heredity
65	210	127	89 ± 4.7	123 ± 6.2

As may be seen, the number of cases of osteogenesis imperfecta found in the material (127) agrees well with the expected number estimated for dominant heredity (123 ± 6.2), but not with that for recessive heredity (89 ± 4.7).

A calculation made according to Weinberg's sibling method gives the following:

No. of sibships with at least 2 siblings	No. of siblings	No. of cases with o. i.	Frequency of o. i. according to Weinberg's sibling method
50	195	110	204/407 = 0.50 ± 0.04

The figure of 0.50 ± 0.04 is in accordance with that expected for dominant heredity with full penetrance (0.50), but not with that for recessive heredity (0.25).

Regarding the material as a proband-selection (since the collection was based on affected individuals recorded), and calculating the frequency of those affected only among the brothers and sisters of the familial proband cases, the following figures are obtained according to Weinberg's proband method:

No. of sibships	No. of siblings	No. of siblings with osteog. imperf.	Frequency of o. i.according to Weinberg's proband method
35*	125	59	0.47 ± 0.05

(*Of these 35 sibships, 23 were fully investigated, i. e. all siblings were personally examined by the author. 6 cases of the disease [dead], and 13 unaffected members of 12 sibships could not be personally examined. Reliable second-hand information was, however, obtained regarding these individuals.)

With this method also, it is found that the figure obtained (0.47 ± 0.05) is in good agreement with that expected for dominant heredity with full penetrance (0.50).

TABLE 32. *Familial cases of osteogenesis imperfecta with fragile bones and blue sclerotics distributed by sibships.*

Sibship No.	No. of Sibs	No. Affected	Pro-bands	Sib-ship No.	No. of Sibs	No. Affected	Pro-bands	Sib-ship No.	No. of Sibs	No. affected	Pro-bands
1	1	1	0	32	2	2	1	61	5	3	0
2	1	1	1	34	2	1	1	62	6	3	0
4	2	2	0	36	4	2	1	63	10	4	0
5	1	1	1	37	3	2	2	64	6	4	0
7	5	2	1	38	5	1	0	65	3	2	0
8	8	2	1	39	3	1	0	66	5	4	0
9	1	1	0	40	2	2	2	67	7	5	5
10	1	1	1	42	4	2	1	69	3	2	0
11	2	2	2	43	2	2	2	70	3	1	0
12	3	2	1	44	2	1	1	71	4	2	0
13	1	1	1	46	2	1	1	72	1	1	1
14	7	5	2	47	2	2	2	73	1	1	0
15	1	1	1	48	2	2	2	74	3	1	0
17	2	1	1	50	2	2	1	75	9	6	0
18	4	2	2	51	3	2	1	76	4	1	0
22	1	1	1	52	2	1	1	77	2	2	1
23	6	3	1	53	1	1	0	78	4	2	1
24	1	1	1	54	10	3	2	79	1	1	1
26	3	1	1	55	3	3	1	80	1	1	0
27	2	1	0	56	2	2	0	81	4	3	0
28	4	3	1	59	4	3	0	87	4	1	0
31	1	1	1	60	4	3	0				
Totals	58	36	21		66	41	22		86	50	9
Grand total									210	127	52

The number of probands indicates the number of times the sibship was independently ascertained. The sibships for which this number is 0 were ascertained through some proband in a previous or in a following generation. Definition of familial cases is found on page 6.

TABLE 33. *Number of affected and normals within different families.*

Sib-ship	Affected		Normal		Transmitter		Sib-ship	Affected		Normal		Transmitter		Sib-ship	Affected		Normal		Transmitter	
No.	Male	Fem-ale	Male	Fem-ale	Father	Mother	No.	Male	Fem-ale	Male	Fem-ale	Father	Mother	No.	Male	Fem-ale	Male	Fem-ale	Fath.	Moth.
1	1	—	—	—	—	1	32	1	1	—	—	1	—	61	3	—	1	1	1	—
2	1	—	—	—	1	—	34	1	—	1	—	—	1	62	1	2	2	1	1	—
4	1	1	—	—	—	1	36	1	1	2	—	1	—	63	1	3	2	4	1	—
5	—	1	—	—	1	—	37	—	2	—	1	—	1	64	1	3	2	—	—	1
7	2	—	2	1	1	—	38	1	—	2	2	—	1	65	—	2	—	1	1	—
8	—	2	1	5	1	—	39	—	1	1	1	1	—	66	2	2	—	1	1	—
9	—	1	—	—	1	—	40	2	—	—	—	—	1	67	3	2	2	—	1	—
10	1	—	—	—	—	1	42	1	1	1	1	—	1	69	2	—	—	1	—	1
11	—	2	—	—	—	1	43	—	2	—	—	1	—	70	1	—	2	—	—	1
12	1	1	—	1	1	—	44	—	1	1	—	—	1	71	2	—	2	—	1	—
13	1	—	—	—	1	—	46	1	—	—	1	—	1	72	—	1	—	—	—	1
14	1	4	1	1	—	1	47	1	1	—	—	—	1	73	—	1	—	—	1	—
15	1	—	—	—	—	1	48	1	1	—	—	1	—	74	1	—	2	—	—	1
17	—	1	1	—	1	—	50	1	1	—	—	—	1	75	4	2	1	2	—	1
18	2	—	1	1	—	1	51	1	1	1	—	—	1	76	—	1	1	2	1	—
22	—	1	—	—	—	1	52	1	—	1	—	1	—	77	1	1	—	—	1	—
23	2	1	—	3	—	1	53	1	—	—	—	—	1	78	1	1	1	1	—	1
24	—	1	—	—	1	—	54	2	1	3	4	1	—	79	1	—	—	—	1	—
26	1	—	1	1	1	—	55	2	1	—	—	—	1	80	1	—	—	—	—	1
27	—	1	1	—	—	1	56	1	1	—	—	—	1	81	3	—	1	—	1	—
28	1	2	—	1	—	1	59	3	—	1	—	—	1	87	1	—	1	2	—	1
31	1	—	—	—	1	—	60	—	3	—	1	—	1							
Totals	17	19	8	14	11	11		22	19	14	11	7	15		29	21	20	16	12	9
Grand total															68	59	42	41	30	35

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Thus, whether methods are used which require that the material be regarded as complete, or methods which make correction for the proband selection, it is found that osteogenesis imperfecta, diagnosed according to the criteria used here, is transmitted in the way expected by a dominant gene with a high and probably complete degree of penetrance.

b) *Sex ratio.* If a disease is due to an autosomal gene the two sexes are affected in equal numbers. This should also apply to the affected parents, who have transmitted the disease to their children.

As may be seen in Table 33, in the 65 sibships the ratio of males affected: females affected = 68:59 = 1.15.

Among the affected parents of these sibships, the ratio of men: women = 30:35 = 0.86.

The deviations from the expected sex ratio (1:1) are not significant. Because of the small size of the material, no consideration was taken of age in calculating the sex ratio.

To summarize, it may be stated that in the greater part of the material, where osseous fragility occurs together with blue sclerotics, and in more than one generation, it is found, in an assessment of the penetrance and sex ratio, that the material satisfies the criteria for a mode of inheritance due to a single, dominant, rare, autosomal gene with complete penetrance.

2. *Familial cases with bone fragility not combined with blue sclerotics, in two or more generations*

This group comprised only three different pedigrees; in these are included 7 carefully examined sibships consisting of 21 persons, of whom 9 were shown to be suffering from bone fragility without associated blue sclerotics. Because these sibships are exceptional, and differ from the rest of the material, it is of interest to describe them in more detail.

Sibship No. 35. The father of this sibship, aged 48 years (35:F), appears to be a sporadic case. According to information from himself and his three brothers and sisters, there had been no tendency to fractures either in their parents (who were dead), or in the rest of the family. The father's brothers and sisters revealed no signs of osteogenesis imperfecta upon examination. The

father had had 7 fractures between the ages of 5 and 14 years, and these had occurred without any excessive strain, e. g. when walking or turning round. Examination revealed no deformities, the sclerotics were of normal colour, his hearing was good, and there was no hyperlaxibility. The mother (wife) was healthy. The sibship consisted of 2 brothers. The elder of these (No. 35:1), who was 15 years old, had broken his left shoulder at 11 years, and his right lower leg at 14 years, both fractures being caused by moderate trauma. Examination showed no evidence of osteogenesis imperfecta. In consideration of the fact that there was moderate trauma on the occasion of both fractures, this case was regarded as uncertain, and was not denoted as osteogenesis imperfecta. The younger brother, 11 years old (No. 35:2), had, on the other hand, had 3 fractures between the ages of 2 1/2 and 10 years, caused by inadequate force, and this case was interpreted as one of bone fragility. Examination revealed normally coloured sclerotics, good hearing, and no hyperlaxibility.

Sibship No. 25. The father of this family, aged 60 years (No. 25:F), stated that he had had poor hearing since birth, and that at the age of 35 years he had sustained a lower leg fracture, quite unjustifiably, while he was carrying a heavy load. Examination revealed bilateral deafness, but otherwise no signs indicating osteogenesis imperfecta. He stated that his mother also suffered from deafness, but that he knew of no tendency to fractures in either of his parents. Of the 5 offspring, No. 1, a 31 year old man, had had three arm and leg fractures due to completely inadequate trauma between the ages of 2 and 17 years. He had also had back trouble, and exhibited a moderate degree of kyphoscoliosis. His teeth also showed changes typical of those found in osteogenesis imperfecta, with discoloration and peeled enamel. The sclerotics appeared to be of normal colour, and his hearing was good.

No. 3, a 25 year old man, had had altogether 9 arm and femoral fractures, caused by very slight trauma, between the ages of 8 and 21 years. He, like his brother, had dental changes typical of osteogenesis imperfecta. He also had slight deafness, but stated that he had often had earache as a child, so the hearing damage could not with certainty be associated with the bone fragility. The sclerotics were of normal colour. Nos. 2 and 4 (brothers), and No. 5 (a sister), had had no fractures.

Sibships Nos. 82—86. These sibships all belonged to the same pedigree, and the tendency to bone fragility could be traced back to a sibship of 8 siblings, of whom only No. 7, a 78 year old woman, was still alive. She had never had fractures, and showed no signs of osteogenesis imperfecta. Her children were said to have had no fractures. Definite information was obtained that Nos. 3 and 6 had had repeated fractures. A son and a grandson of No. 3 were found to have had several fractures of inadequate trauma, but otherwise showed no evidence of the disease. Both sons and a grandson of No. 6 were also found to have had repeated fractures due to inadequate force. This grandson was most badly affected, having had repeated fractures, and such pronounced deformities of the femur and lower leg, that he had to use an invalid chair. No other signs of osteogenesis imperfecta were found in the members of this pe-

digree, either in the form of blue sclerotics, deafness, specific dental changes or hyperlaxibility.

The most essential trait in these three families was that the disease was manifested mainly in the form of bone fragility without any simultaneous occurrence of blue sclerotics. In sibship No. 25, dental changes typical of osteogenesis imperfecta were also found. Whether deafness, both in the father and paternal grandmother of this sibship, was also related to osteogenesis imperfecta, is uncertain. In both of the other families, bone fragility was the only sign of the disease.

The inheritance in these pedigrees does not contradict the supposition of a dominant gene. The material is too small for any significance to be ascribed to the predominance of the male sex. The main problem is, how may the absence of blue sclerotics throughout the group be explained. One possibility might be that the fragility in this group has a different genetic basis from that in the rest of the material. Another is that the same gene is affected in this group as in the rest of the material, where the gene mutation gives a pleiotropic effect resulting in both bone fragility and blue sclerotics, but that the gene milieu in these few families has modified the character of blue sclerotics. According to Caspari (1952), "different pleiotropic effects of the same genes may exhibit different degrees of dominance or recessivity in the heterozygote, and are affected differently by genetic modifiers and environmental conditions". The fact that in this group the sign of blue sclerotics is suppressed in several generations of individuals with bone fragility, would in this case mean that the modifying gene or genes were more or less closely linked with the gene for osteogenesis imperfecta.

The fact that blue sclerotics are absent for several generations, however, makes the hypothesis of genetic modifiers somewhat questionable. The modifying effect might be expected to break down within some generations, unless there is a close linkage between the gene of osteogenesis imperfecta and the modifier.

Another explanation might be that the new mutations are not always identical from the point of view of biochemical genetic function. Recent investigations have revealed that the genes are complex (see Pontecorvo 1958). Within these complex genes, called cistrons, there may be hundreds of mutational sites. So called identical mutations within the same classical gene are thus probably never quite structurally identical. This

might offer an explanation for the absence of blue sclerotics in some cases of osteogenesis imperfecta, namely that the mutation in these cases may not have affected the site controlling this trait. This view seems to be in accordance with Seedorff's hypothesis concerning several closely linked genes.

3. Familial cases with one or more affected siblings, whose parents revealed no signs or symptoms of osteogenesis imperfecta

This group comprised 5 sibships of altogether 25 persons, of whom 14 showed evidence of osteogenesis imperfecta.

As such cases are both rare and genetically difficult to explain, it seems justifiable to give a somewhat detailed account of each of the individual sibships in this group.

In two of the five sibships, the osteogenesis imperfecta cases were of the lethal (so-called congenital) type, while only surviving (so-called tardive) cases were found in the other three.

The lethal cases.

Sibship No. 95. The sibship consisted of 7 children. No. 3 (born in 1932), No. 4 (born in 1933) and No. 6 (born in 1938), all boys, showed typical signs of the disease at birth, with multiple fractures, deformed extremities, cranial ossification disturbances, and blue sclerotics. No. 3 died at 2 1/2 months, No. 4 at 5 1/2 months and No. 6 at 12 1/2 months. Histological examination verified the diagnosis of osteogenesis imperfecta. Post mortem examination also showed an open foramen ovale in No. 3, stenosis of the aortic arch in No. 6, and bronchopneumonia in all three cases. Both the parents and the four remaining siblings (2 brothers and 2 sisters) were examined in 1957 during the field investigation, and it was found that none of them had had fractures or exhibited any blueness of the sclerotics beyond normal variations. The mother had had a congenital subluxation of the right hip since childhood, but had otherwise always been healthy. There was no information concerning the paternal or maternal grandparents which indicated osseous fragility. The parents were not related. The age of the mother at the birth of the affected children was 31, 32 and 37 years respectively; the father was one year younger.
Sibship No. 98. Both parents had always been healthy, and had never sustained fractures. This also applied to their parents. The parents were not related. No evidence of osteogenesis imperfecta was found in either of them during the 1957 investigation. The first child, a girl, born 1948, died at the age of 13 months, and the second, a boy, born 1951, died one hour post partum.

Both children had multiple fractures, pronounced deformities and cranial ossification disturbances at birth. The age of the mother at the birth of the two children was 25 and 28 years respectively, and the father was 4 years older.

The surviving cases.

Sibship No. 96. The mother, aged 70 years, showed no signs or symptoms of osteogenesis imperfecta on examination in 1957. Neither the father, who was dead, nor the paternal or maternal grandparents had shown any evidence of osteogenesis imperfecta, according to reliable information. The parents were not related. No. 4 in the sibship, a 40 year old man, a proband, who was examined in 1957, had had numerous fractures from the age of 2 years, estimated at at least 75. These were sometimes produced only by movement in bed, and were localized to the clavicles, ribs and extremities. He had pronounced deformities of the extremities, and a scoliotic, contracted spine. The sclerotics were of normal colour. He was severely disabled, and used an invalid chair. No. 3, who died at 6 years, and No. 6, who died at 17 years, had both had repeated fractures from the age of 2 years, according to the information obtained. In both cases the fractures had often been produced by quite insignificant movements. They had therefore been almost permanently confined to bed. Nos. 1 and 2, who were also examined in 1957, showed no signs or symptoms of osteogenesis imperfecta, and according to reliable information this also applied to No. 5.

Sibship No. 94. The parents, who were dead, had not shown any signs or symptoms of osteogenesis imperfecta, according to reliable information. No. 4 in the sibship, a 51 year old woman, had had repeated fractures of both the upper and lower extremities since before the age of 1 year. On examination she was found to have pronounced deformities of the femur and spine, she could only walk with difficulty, and was denoted as fairly severely handicapped. The sclerotics were of normal colour.

No. 2, a girl who died at 13 years, had, according to information obtained from No. 6, sustained repeated fractures and had never been able to walk, but as far as was known she had not had blue sclerotics. Information was obtained from a hospital that she had been treated as a case of osteogenesis imperfecta, but no further information was found. Nos. 1 and 5 in the sibship showed, on examination, no signs or symptoms of osteogenesis imperfecta.

Sibship No. 97. This sibship comprised 6 siblings, all of whom, like the parents, were examined during the field investigation of 1957. The mother, aged 56 years, had sustained a fracture of the left lower leg during a bicycle accident at the age of 18 years, but otherwise she had always been in good health. Examination revealed some deafness in the left ear, of which she had been aware for several years, but on the right side her hearing was good. She showed no other evidence which could indicate a condition of osteogenesis imperfecta. As far as she knew, there had been no known disease among her parents or her 5 half brothers and sisters. The father (her husband) who had had a mental

disorder, was 63 years of age at the time of examination. He had never had fractures and showed no signs or symptoms of osteogenesis imperfecta. Of the 6 children, Nos. 1, 4, 5 and 6 had all had repeated fractures.

No. 1, a 31 year old woman, was found to have had about 12 fractures of the femur and lower leg since the age of 1 1/2 years. She had pronounced deformities of the femur and lower leg, and the spine was greatly contracted. She had fairly severe impediment of movement, and could only move about with the help of crutches. Her sclerae appeared to have a slightly blue tinge, but were within normal limits.

No. 4, a 24 year old woman, had had several fractures of the femurs, ribs and vertebrae since about the age of 2 years. Previous X-ray examination had shown old vertebral fractures, vertebral compressions and "fish vertebrae formation". Examination revealed a somewhat contracted spine with slight scoliosis, but otherwise no deformities. There was no movement handicap. A blueness of the sclerotics which was more pronounced than the normal, was seen.

No. 5, a 19 year old woman, had had 5 fractures between the ages of 3 and 12 years. She showed no deformities and no handicap to movement. The sclerotics had a slightly blue tinge, but within normal variations.

No. 6, a 14 year old boy, had had about 15 fractures of the femur and lower leg since the age of 4 years, which resulted in such severe deformities of the legs that he had been unable to walk since he was 9 years old. The sclerotics appeared abnormally blue.

No. 5 also had a moderate degree of deafness in the left ear, which she stated had begun after a blow on the ear while at school. The other siblings had good hearing. No. 5 also showed dental changes typical of osteogenesis imperfecta, in that the incisors were small and yellowish brown. Extensive dental caries were found in the other siblings. Siblings Nos. 2 and 3 showed no signs or symptoms of osteogenesis imperfecta.

The family last described, No. 97, is worthy of mention in several respects: (1) There was no definite evidence of osteogenesis imperfecta in the parents. (2) In two of the affected siblings the colour of the sclerotics was abnormally blue, while in the other two it was regarded as normal. (3) The degree of severity, assessed according to the handicap to movement, showed an unusual degree of variation in this family, the mildest cases having no handicap, and the severe cases severe handicap. (4) It is of especial interest for the interpretation of the mode of inheritance in this family, that a blood group examination showed that one of the affected siblings (No. 97:5) could not have been a daughter of the family father (No. 97:F). This will be discussed further, below.

All five of the sibships described above, in which two or more cases

of osteogenesis imperfecta occurred in each, but where the parents showed no signs of the disease, suggest the possibility of a recessive gene effect. Those affected would, in this case, be homozygous, i. e. they would possess a pair of abnormal genes, and the normal parents would be heterozygous and healthy, but capable of transmitting the condition due to the possession of a single recessive gene. Herndon (1956), who also describes similar sibships with two or more cases of typical osteogenesis imperfecta, in whose parents no signs of the disease were found, points out that a postulated recessive gene for osteogenesis imperfecta must be rare in the general population. Marriage at random between two unrelated heterozygotes would occur extremely seldom. It would therefore be expected that these affected cases would most often be born in marriages between cousins. In actual fact, however, "cousin marriages" have seldom been found among the parents of patients with osteogenesis imperfecta. (No such marriages were found in the present investigation.) On the basis of this argument, Herndon draws the conclusion that even if the possibility of recessive heredity cannot in this way be excluded, it is nevertheless unlikely. He also points out that it would seem more likely that one of the parents of such a sibship is a subclinical carrier of a dominant gene, and that this gene for some reason does not manifest itself (failure of penetrance).

This supposition is supported by a closer study of sibship No. 97, for which recessive heredity is found to be practically excluded.

With the aim of studying linkage relationships in osteogenesis imperfecta, blood group determinations were made whenever possible, on the families examined, at the time of the field investigation. In analysing these data, it was found that No. 97 : 5, a 19 year old woman with clearly manifested bone fragility and slender body build, could not have been the daughter of the family father, No. 97 : F. This was excluded by both the MN and the Rh systems. (See Fig. 2.) For the other children in the family, the paternity was not, however, contradicted by the serological examinations. If a recessive heredity actually exists in this family, a recessive gene must thus be presupposed, not only in both the husband and wife (97 : M and 97 : F), but also in the unknown father of 97 : 5. The possibility of such a coincidence for such a rare recessive gene can almost certainly be excluded. It is evident that the woman, 97 : 5, must have inherited the trait of osteogenesis imperfecta from her mother, and that the mother in this family must have been the carrier

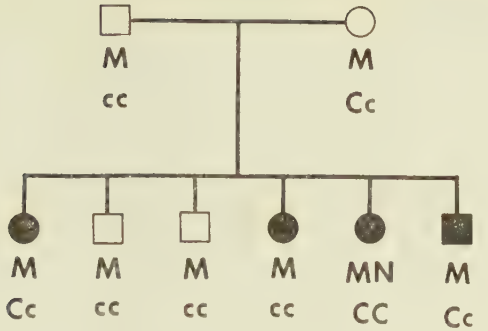

Fig. 2. Pedigree of family No. 97. □ = male, ○ = female. Solid symbols designate affected individuals, M, N, C and c different bloodgroups.

of a dominant gene, although she did not exhibit definite symptoms of the disease. On reaching this conclusion it seems probable that the lower leg fracture sustained by the mother during a cycling accident at the age of 18 years, and the left-sided deafness which she had noticed for several years, may in fact be manifestations of the disease, although these symptoms in themselves, however, are insufficient for a diagnosis to be made.

An example has also been given previously (No. 34: M, p. 129—130) of the wide variations in the expressivity of the disease, and it seems therefore that in rare cases certain features of the disease can be entirely absent.

The variation in expressivity which has often been demonstrated, even within a particular family, may be explained as being primarily due to a varying gene milieu, i. e. that other parts of the genetic constitution are such, that they more or less strongly modify the effect of the defective gene. This gene milieu varies, of course, among different individuals, and may have positive or negative effects. It is probable that extrinsic factors (external environment) also, may play a part in the degree of severity, and the course of the disease (cf. section on exacerbating factors, clinical section).

The unique occurrence of cases of bone fragility with abnormally blue sclerotics, and those of bone fragility with sclerotics of normal colour in the same family, might be explained by the concept "that different pleiotropic effects of the same gene may be affected differently by genetic modifiers and environmental conditions". (Cf. quotation from Caspari, p. 136.)

C. The genetic interpretation of sporadic cases

As was pointed out by Neel and Schull (1954, p. 138), "many identical, or shall we say clinically indistinguishable, phenotypes arise as a result of mutation at any one of several loci. We can never be certain in man that the sudden appearance of a given trait is always due to mutation at the same locus, or, in sporadic cases of certain diseases, that it is due to germinal, rather than somatic, mutation. However, on the basis of comparative genetics and developmental physiology, we can at least select for study specific phenotypes which, with a high degree of probability, are due to changes involving a particular locus. Thus most, if not all, pedigrees of achondroplasia or hemophilia or retinoblastoma are probably due to mutation of the same locus, whereas this is not so for less specific entities, such as hypertension or diabetes". Crowe, Schull and Neel (1956) state generally that, when one is dealing with a dominantly inherited disease occasioned by a gene with a high level of penetrance, it is customary to attribute the occurrence of sporadic cases of the disease to mutation. Although practical problems may arise in assuming that sporadic cases of diseases, known to have an inherited basis in some families, represent mutations, the same authors find the assumption of mutation justified when:

1. The offspring of sporadic cases are affected and in a ratio compatible with dominant heredity,
2. There exists no evidence of an effect of maternal age and/or parity on the distribution of sporadic cases, and
3. The sporadic case is clinically indistinguishable from the familial.

The sporadic cases in the present material will be studied here on the basis of these three criteria.

1. The occurrence of osteogenesis imperfecta among the progeny of sporadic cases

As previously mentioned (page 128), 72 of the 266 cases of Swedish birth, in our series, were denoted as sporadic. Nine of these sporadic cases had given birth to children, 18 children surviving in all. Of these 18 children, 9 (50 %) showed signs of the disease. Although this part of the material is too small to offer any statistically satisfactory evidence, it seems,

nevertheless, that the frequency of the disease among these children of sporadic cases does not deviate from the rest of the material, but supports the concept of a dominant heredity. This supports the view that these sporadic cases are genetically of the same nature as the familial cases.

From a hereditary aspect, it is impossible to determine whether the sporadic cases who did not give birth to children with signs of osteogenesis imperfecta, are genetically of the same nature as the familial cases. There is nothing, however, to contradict this concept.

2. Maternal age and birth rank

If a disease is exclusively of a genetic nature, its occurrence should have no relationship with the age of the mother at the birth of the child, and neither should the disease have any relation to the parity of the mother. If it is found, for example, that the first child is more often affected, this would seem to indicate that birth trauma is a contributory factor.

Maternal age. In Table 34 the sporadic cases are distributed according to the age of the mothers at the birth of the affected children. The

TABLE 34. *Sporadic cases of osteogenesis imperfecta distributed by maternal age.*

Age of Mother	Lethal cases		Viable (tardive) cases		All cases	
	Observed	Expected	Observed	Expected	Observed	Expected
—19	—	0.3	2	1.0	2	1.3
20—24	2	3.0	7	9.3	9	12.3
25—29	4	4.6	10	14.3	14	18.9
30—34	3	4.0	17	12.4	20	16.4
35—39	5	2.8	10	8.7	15	11.4
40—44	2	1.2	4	3.9	6	5.1
45—	—	0.1	—	0.4	—	0.6
Total	16	16.0	50	50.0	66	66.0
Mean age	32.3	30.7 ± 1.56	30.6	30.7 ± 0.88	31.0	30.7 ± 0.77
P		> 0.30		> 0.90		> 0.60

table gives the sporadic cases, both divided into lethal and surviving cases, and as the total of these two categories. The expected age distribution has been calculated from the age distribution of married women at childbirth during the period 1901—1951, in the whole country. No significant deviation from the expected values can be established.

Parity. In investigating the possible effect of parity on the occurrence of sporadic cases, only families with at least 2 children can be included in the investigation.

The distribution of different parities for the sporadic cases was first tested according to the method of Weinberg and Schulz (cf. Schulz 1936 and Böök and Rayner 1950). In Table 35 the sporadic cases have been arranged according to parity, both with lethal and surviving cases separately, and together. In no group did the distribution observed deviate significantly from that expected according to this method.

According to a method reported by Penrose (1954), the possible effect of maternal age and parity combined, on the occurrence of spo-

TABLE 35. *Sporadic cases of osteogenesis imperfecta distributed by birth rank.*

Birth rank	Lethal cases		Viable (tardive) cases		All cases	
	Observed	Expected	Observed	Expected	Observed	Expected
1	3	4.8	5	11.9	8	16.7
2	4	4.8	18	11.8	22	16.6
3	3	2.8	3	5.9	6	8.6
4	3	1.8	5	4.5	8	6.3
5	2	1.1	5	3.5	7	4.6
6	1	0.4	3	2.3	4	2.8
7	—	0.3	2	1.3	2	1.6
8	—	—	1	0.6	1	0.6
9	—	—	—	0.1	—	0.1
10	—	—	—	0.1	—	0.1
Total	16	16.0	42*	42.0	58	58.0
χ^2	1.770		8.879		9.432	
D. f.	1		4		5	
P	> 0.10		0.05—0.10		0.05—0.10	

* excl. 8 families with one child

TABLE 36. *Observed and expected numbers in each birth rank and maternal age groups in 58 sibships containing sporadic cases of osteogenesis imperfecta.*

Birth rank		Maternal age, years —24	25—29	30—34	35—39	40—	Total
1	obs.	6	—	2	—	—	8
	exp.	7.59	6.37	2.69	—	—	16.65
2	obs.	2	7	8	4	1	22
	exp.	2.36	6.04	5.89	1.86	0.50	16.65
3	obs.	2	1	2	1	—	6
	exp.	1.13	2.07	3.43	1.69	0.33	8.65
4	obs.	—	3	3	2	—	8
	exp.	0.17	0.96	3.79	1.19	0.20	6.31
5	obs.	—	—	2	4	1	7
	exp.	—	0.72	1.00	2.12	0.73	4.57
6	obs.	—	—	—	1	3	4
	exp.	—	0.31	0.51	1.18	0.76	2.76
7	obs.	—	—	—	1	1	2
	exp.	—	—	0.14	0.63	0.83	1.60
8—10	obs.	—	—	—	1	—	1
	exp.	—	—	—	0.23	0.57	0.80
Total	obs.	10	11	17	14	6	58
	exp.	11.25	16.47	17.45	8.90	3.92	58

radic cases, can also be assessed. Using this method (Table 36), the deviation found in our material between observed and calculated frequencies in the different classes, is close to the 5 per cent significance level ($\chi^2 = 4.37$; D. F. = 1; $0.02<P<0.05$). As may be seen in the table, there is a high frequency of low birth rank (i. e. birth rank 2), combined with a tendency to a higher age in the mother at the child's birth.

It appears rather peculiar that the second child is so greatly over-represented compared with the first. It is necessary to study more closely the parity and maternal age in the 15 families with only two children. It is found, that in ten of these families the affected child is the second, and that 7 of the mothers in these 10 families were 30 years of age or over at the birth of the affected child. The probability that these conditions are obtained at random, is quite small ($0.05<P<0.10$). A possible explanation is that to a certain extent the parents decided to limit the number of children when it was discovered that the second child had osteogenesis imperfecta, and that this probably applied more to families in which the mother was older.

It may thus be said, in summary, that neither the age of the mother nor the parity of the child has with certainty been shown to have any effect on the distribution of sporadic cases of osteogenesis imperfecta.

3. Comparison between the clinical picture of the sporadic cases and that of the familial cases

In Table 37 the occurrence of the most common symptoms in osteogenesis imperfecta in sporadic and in familial cases is summarized. The numbers of cases with different degrees of handicap within these groups are also compared.

Considering first the degree of handicap, which to some extent reflects the degree of severity, the incidence of severe handicap is significantly higher among the sporadic cases. This does not, however, invalidate the view that the sporadic and familial cases are genetically similar, as the following quotation from Neel and Schull (1954, p. 141) explains: "Penrose was the first to point out that, with regard to a trait produced by a dominant gene with rather deletarious effects, persons with negative family histories (which presumably were due to mutation) were inclined to be more severely affected than persons with positive family histories. This is explained on the basis that the difference between mildly and severely affected persons is often a matter of genetic modifiers. Severely affected persons are not likely to reproduce. It is therefore the mildly affected who propagate, transmitting to their offspring both the principal gene and (sometimes) the favourable modifiers."

TABLE 37. *Comparison between the occurrence of different symptoms in sporadic and familial cases.*

Signs and symptoms		Sporadic cases (53)		Familial cases (137)		Difference %
		No.	Per cent of 53	No.	Per cent of 137	
Fractures		53	100.0	129	94.2	5.8 ± 2.0
Deformities		47	88.7	83	60.6	28.1 ± 6.0
Abnormal shape of skull		21	39.6	8	5.8	33.8 ± 5.3
Blue sclerotics		36	67.9	124	90.5	— 22.6 ± 6.9
Arcus corneae		9	17.0	46	33.6	— 16.6 ± 6.6
Deafness		11	20.8	32	23.4	— 2.6 ± 6.6
Hyperlaxibility		27	50.9	58	42.3	8.6 ± 8.1
Dental changes		17	32.1	12	8.8	23.3 ± 6.9
Overliability to bruises		13	24.5	46	33.6	— 9.1 ± 7.2
Degree of physical handicap	None	16	30.2	106	77.4	— 47.2 ± 7.2
	Slight	11	20.8	21	15.3	5.5 ± 6.4
	Fairly severe	9	17.0	8	5.8	41.8 ± 7.2
		26	49.1	10	7.3	
	Severe	17	32.1	2	1.5	

Another possible contributory cause to the fact that sporadic cases in a material such as this are found on an average to be more severely affected than familial cases, may be that mild sporadic cases are not so frequently diagnosed and reported as mild familial cases; in other words, that mild sporadic cases are to a certain extent underrepresented in the material.

The fact that the frequency of deformities and abnormal skull shape predominate among the sporadic cases, is a logical consequence of the predominance of the more severe cases in this group, since these symptoms are connected with an increasing degree of severity. This also applies to the characteristic dental changes. As regards the deformities, it should be noted that they all appear to be of the same type, and that there seems to be no apparent difference between deformities in sporadic

or familial cases, or in cases with blue sclerotics or with sclerotics of normal colour.

The significant difference for the occurrence of blue sclerotics between the two groups can also be presumed to be connected with the difference in degree of severity between sporadic and familial cases. Since the diagnostic criteria must necessarily be more stringent if the sclerae are normally coloured, it follows that it is probable that of the cases with sclerotics of normal colour, a relatively higher proportion will be severe than in those with blue sclerotics, since milder sporadic cases with normal sclerotics will more frequently avoid classification as osteogenesis imperfecta than will cases with blue sclerotics.

It is therefore not unexpected to find a relative predominance of normal sclerotics among the more severe, sporadic cases, who seldom form families, and a predominance of blue sclerotics among the milder cases, who form families and have children, who, when they inherit the disease, most often acquire it in a milder form.

No difference in the symptomatic picture between sporadic and familial cases, which might indicate that sporadic cases were genetically dissimilar (i. e. could not be regarded as being due to a mutation of the same gene as in the familial cases), was thus observed in the present material.

With reservations for the uncertainty always attached to mutation studies, it thus seems valid, after examining the sporadic cases in this series on the basis of the criteria cited on page 142, to regard them as due to mutations of the same genetic type as the familial cases.

D. Comparison between the clinical picture of cases with sclerotics of normal colour and that of cases with blue sclerotics

As mentioned previously, Bell (1928) considered that cases with both bone fragility and blue sclerotics and those with bone fragility alone, could not be regarded as genetically homogeneous.

If in the present series a direct comparison is made between these two groups, in the same way as between sporadic and familial cases (see Table 37), the figures are obtained as shown in Table 38. The

TABLE 38. *Comparison between the occurence of different symptoms in individuals with sclerotics of normal colour and that of individuals with blue sclerotics in the total material.*

Symptoms		Cases with sclerotics of normal colour (30)		Cases with blue sclerotics (160)		Difference %
		No.	Per cent of 30	No.	Per cent of 160	
Fractures		30	100.0	152	95.0	5.0 ± 1.7
Deformities		26	86.7	104	65.0	21.7 ± 7.3
Abnormal shape of skull		7	23.3	22	13.8	9.5 ± 8.2
Arcus corneae		1	3.3	54	33.8	— 30.5 ± 5.0
Deafness		3	10.0	40	25.0	— 15.0 ± 6.5
Hyperlaxibility		6	20.0	79	49.4	— 29.4 ± 8.3
Dental changes		10	33.3	19	11.9	21.4 ± 9.0
Overliability to bruises		—	—	59	36.9	—
Degree of physical handicap	None	12	40.0	110	68.8	— 28.8 ± 9.7
	Slight	1	3.3	31	19.4	— 16.1 ± 4.5
	Fairly severe	7	23.3	10	6.3	44.8 ± 9.4
		17	56.7	19	11.9	
	Severe	10	33.3	9	5.6	

deviations which are found here, as regards degree of handicap and deformities, can be explained in the same way as for sporadic and familial cases, namely, that in the group consisting of cases with sclerotics of normal colour, there is, as in the sporadic group, a certain degree of selection of more severe cases. No demonstrable difference in the frequency of deafness can be established. There is a significant difference, however, as regards arcus corneae, hyperlaxibility, and also the tendency to bruising, in that these symptoms occur more often in cases with blue sclerotics than in cases with sclerotics of normal colour. Particularly concerning arcus corneae, but also as regards the other two symptoms, it seems reasonable to suppose that they are due to changes in the connective tissue essentially similar to that responsible for the blue tinge (= translucency) in the sclerotics, and are therefore possibly influenced by the same modifying genes.

It appears that the differences thus observed between cases with blue sclerotics and those having normal sclerotics might be explained without necessarily assuming that these are two genetically different diseases.

The fact that the two different categories were found, as an exception, in one particular family, viz. family No. 97, where in two cases the sclerotics were denoted as blue, and in two cases normal in colour, also contradicts the concept that differences in the translucency of the sclerotics in different cases of fragility necessarily indicate a genetic heterogeneity.

In summary, it may probably be said that a genetic homogeneity cannot be established, but, on the other hand, no definite grounds for heterogeneity were found.

E. Interfamilial and intrafamilial variability

By "interfamilial variability" in this connection is meant differences in the symptomatology between different families, and by "intrafamilial variability" is meant the difference between individuals in any one family.

It is of especial interest to know how the degree of severity of the disease, as regards bone fragility, varies within and between different families, and particularly the extent to which this can vary from parents to children. It has been shown previously (pp. 78—79), that the degree of handicap can be regarded as constituting a satisfactory measure of the degree of severity of the disease. Of the different families in this material, it was possible to examine 31 with cases of osteogenesis imperfecta in two or more generations. In studying these families with the view to discovering how the degree of severity of the disease, measured by physical handicap, varied within these families, especially from generation to generation, the following was found:

1. In 17 families the character of the disease remained unchanged at the same degree of severity, both within each generation and from one generation to another.

2. Within 12 families the physical handicap varied between two close degrees of severity. In 8 of these, succeeding generations kept within the same handicap group as the preceding generation, or exhibited some-

what milder forms. In 4 families, a shifting to the next higher degree of handicap severity was observed in a later generation.

3. In 4 families, varying degrees of physical handicap were found, spread over three degrees of severity, and in three of these families one case was found in a later generation with more than one degree higher severity of handicap than that occurring in preceding generations.

To judge by the conditions in these families, it thus appears that the degree of severity of the disease remains the same on the whole within any one family, and that children of parents with osteogenesis imperfecta, if they inherit the disease, exhibit approximately the same degree of severity as their parents, although slight deviations may occur to the next degree milder or more severe handicap group. Only in exceptional cases (in this series 3 out of 131 cases = 2.3 %) does the severity increase more than one degree (measured by degree of handicap) in a succeeding generation.

This applies to cases belonging to "several generation families", in which the disease occurs as a rule in one of the milder forms. Individuals with the most severe degree of handicap were not found in these families, but only among the solitary cases, and in three of the families in which several children contracted osteogenesis imperfecta although the parents showed no evidence of the disease. There is reason to suppose, however, that the rule concerning the retention of the degree of severity from one generation to another also applies, if a patient with a severe form of the disease reproduces. In the family described by Ekman (1788), several generations exhibited pronounced deformities, all obviously of approximately the same degree of severity. Seedorff describes a woman, clearly a severe invalid-chair case, who gave birth to a child with a lethal form of the disease.

In conclusion it may be stated, that whether a patient has the disease in a severe or a mild form, the rule — with few exceptions — seems to be that the children, when they inherit the gene, acquire the disease with a degree of severity similar to that of the parents. The degree of severity within any one family generally shows, therefore, only small variations, but can vary greatly from family to family.

No grading of the blue shade in blue sclerotics in different individuals has been carried out on the present material. It has been established, however, that the blue tinge can vary greatly, even within any one family. There does not seem to be any correlation between the degree

of bone fragility and the intensity of the blue colour in the sclerotics. Intensely blue sclerotics may occur simultaneously with pronounced bone fragility, and vice versa. When, however, blue sclerotics occur in a family with bone fragility, as a rule all the affected individuals in that family have this sign to a more or less pronounced degree; and when a case of osteogenesis imperfecta with normally coloured sclerotics occurs in a family, blue sclerotics are not usually found in any of the other members suffering from the disease. As previously mentioned, sibship 97 is the only exception to this rule (see p. 150), in which the sclerotics of two of the affected siblings were denoted as blue, the other two being of normal colour.

A systematic assessment of the inter- and intrafamilial variability of deafness is difficult because of the varying age of onset of this symptom. It seems certain, however, that strong intrafamilial variations may be found. This is shown, for example, in sibship 75 of this series, where of six affected siblings, two (of ages 58 and 54 years) had pronounced deafness, while the other three examined (61, 46 and 44 years) had normal hearing.

Both arcus corneae and hyperlaxibility and/or liability to distortions, were found to have a greater variability interfamilially than intrafamilially.

The fact that the *inter*familial variability as measured by the degree of handicap is rather large as compared to the *intra*familial one indicates an effect of genetical modifiers. However, the total absence in some families of blue sclerotics over several generations could mean that the major dominant gene was slightly different in some families. This is the same as to say that the mutations occur at different sites within a gene complex (cistron). It should also be mentioned that these mutations, in fact, may be small chromosomal deficiencies with varying length. There are several arguments in favor of the idea that recessive mutations are generally gene mutations in the strict sense while dominant mutations are more likely to be minute chromosomal deficiencies. However, there is so far no way of testing this hypothesis.

F. The geographic distribution of osteogenesis imperfecta in Sweden

The geographic distribution of the place of residence of the 190 investigated cases alive in 1957, is found to follow that of the general population (see Figs. 3 and 4).

On the map in Fig. 5, the country has been divided into 25 regions in agreement with the administrative division of the country into 24 counties and one governorship (the capital of Stockholm). These have been numbered 1—25, beginning in the north. To correspond with this classification, Table 39 gives: A) both the absolute number of recorded and examined individuals alive in 1957, living in different counties, and the corresponding number of individuals with the disease per 100,000 of the whole population, and B) both the number of recorded individuals born during the 13 year period 1943—1955 in different counties, and the corresponding number per 100,000 born in the whole population during the same 13 year period.

As may be seen, both the frequency of those resident, and that of those born, in different counties, varies greatly from county to county. This is explained partly by the rareness of the disease, and partly by the accumulation of affected individuals in certain places, due to the occurrence of single large families with several individuals with the disease. If, however, the counties are classified into three large regions (as in Table 39), comprising I. Norrland counties 1—5, II. Svealand counties 6—13, and III. Götaland counties 14—25, more even frequencies are found. For the frequency of cases based on the place of residence, the figures of 2.05, 3.32 and 2.21 per 100,000 of the population were obtained, and for that of cases born during the period 1943—1955 the figures of 2.69, 4.34 and 3.63 per 100,000 born during those years. These figures show no significant difference between the different parts of the country, as regards the frequency of the disease and the frequency of births, but indicate a relatively even distribution.

In Table 40, the number of cases per 100,000 births in the whole population in the three parts of the country have been divided into sporadic and familial cases. No significant difference is found between the three regions as regards the birth frequency of sporadic cases.

In comparing the occurrence of these individuals in towns and other

Fig. 3. The geographic distribution of the places of residence of the 190 individuals with osteogenesis imperfecta alive and examined in Sweden in 1957. Each dot represents an individual.

Fig. 4. A map of Sweden. Density of population in 1950. Dark squares = densely populated areas with > 2.000 inhabitants. Each black dot represents 2.000 inhabitants of the rural population. (After S.-O. Garland, 1960.)

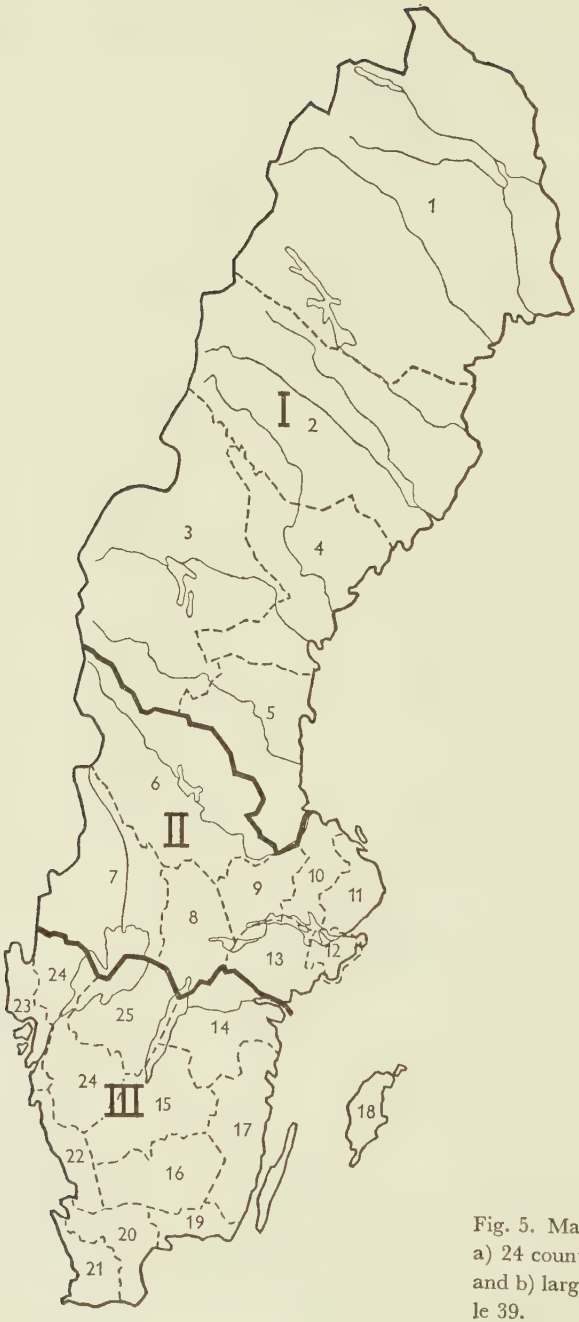

Fig. 5. Map of Sweden divided into a) 24 counties and one governorship and b) larger regions I-III. See Table 39.

TABLE 39. *Geographical distribution of osteogenesis imperfecta in Sweden by counties (1—25) and larger regions (I—III).*

A) According to place of residence 1957.

B) According to place of birth (1943—1955).

Region	County	A. Place of residence (1957)		B. Place of birth (1943—1955)	
		No. of cases	Per 100 000 inhabitants	No. of cases	Per 100 000 births
I. Norrland counties	1. Norrbotten	6	2.35	2	2.79
	2. Västerbotten	6	2.50	3	4.93
	3. Jämtland	—	—	—	—
	4. Västernorrland	7	2.42	2	3.05
	5. Gävleborg	6	2.04	1	1.56
	Total 1—5	25	2.05	8	2.69
II. Svealand counties	6. Kopparberg	6	2.12	4	6.72
	7. Värmland	1	0.34	—	—
	8. Örebro	17	6.56	1	1.87
	9. Västmanland	2	0.89	1	2.10
	10. Uppsala	16	9.77	3	8.30
	11. Stockholm county	11	2.65	2	2.38
	12. Stockholm city	20	2.51	9	5.42
	13. Södermanland	15	6.74	4	8.38
	Total 6—13	88	3.32	24	4.34
III. Götaland counties	14. Östergötland	—	—	4	5.12
	15. Jönköping	7	2.49	4	6.47
	16. Kronoberg	2	1.26	1	2.95
	17. Kalmar	1	0.42	1	1.92
	18. Gotland	1	1.78	—	—
	19. Blekinge	3	2.07	1	3.06
	20. Kristianstad	7	2.71	1	1.76
	21. Malmöhus	12	1.97	7	5.54
	22. Halland	6	3.59	3	8.47
	23. Göteborg and Bohus	20	3.33	—	—
	24. Älvsborg	8	2.16	2	2.60
	25. Skaraborg	10	4.02	3	5.52
	Total 14—25	77	2.21	27	3.63
The whole of Sweden		190	2.58	59	3.70

TABLE 40. *Number of sporadic and familial cases born 1943—1955 in three different regions of Sweden.*

Region	Sporadic cases		Familial cases		Sporadic + Familial cases	
	No. of cases	Per 100 000 births	No. of cases	Per 100 000 births	No. of cases	Per 100 000 births
Norrland	4	1.34	4	1.35	8	2.69
Svealand	11	1.99	13	2.35	24	4.34
Götaland	16	2.15	11	1.48	27	3.63
The whole of Sweden	31	1.94	28	1.76	59	3.70

built up areas, on the one hand, and in sparsely populated areas, on the other, it is found that they are proportionately somewhat more numerous in towns and other built up areas (see Table 42 in the socio-medical section). This may conceivably be connected, at least in part (see Table 55, p. 202), to the fact that this group of individuals is under-represented in the heavier occupations such as farming and agricultural work associated with the country districts, while they are over-represented in the lighter occupations connected with trade (mostly to be found in the towns and other built up areas). Another contributory reason that these individuals tend to live in the towns and other built up areas to a greater extent than the rest of the population may conceivably be that those who are handicapped find it easier there to obtain help and care.

G. Factors possibly influencing the occurrence of mutation

It has been shown previously that in the present material no basis can be found for believing that the maternal age and birth rank have any effect on the occurrence of the sporadic cases, whom it should be justifiable to regard as mutation cases (cf. p. 143 ff.).

The time of year at conception has also been mentioned among other factors which might conceivably play some part in the occurrence of

mutations (cf. Mørch 1941, Falls and Neel 1951, and Neel and Schull 1954). The following shows the distribution according to the month of conception of the 72 sporadic cases in the present material, born between 1890 and 1950, and the expected distribution calculated on the corresponding distribution of all children born in the country during the period 1911—1950:

	Jan.	Febr.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
No. of sporadic cases conceived during that month	15			19			19			19		
	5	6	4	8	7	4	9	2	8	4	9	6
Expected No.	16.9			18.4			18.9			17.8		
	5.7	5.4	5.8	5.9	5.8	6.7	6.5	6.5	5.9	6.0	5.8	6.0

There was no significant deviation in this respect from the rest of the population ($\chi^2 = 10.07$; 11 d. f.; $0.3<P<0.5$).

It was shown that no significant difference could be established between the occurrence of the sporadic cases in different parts of the country. Thus there is no basis for believing that different climatic or other conditions in different parts of the country might have any effect on the mutation frequency.

The general state of health of the parents of the 72 sporadic cases was on the whole good. 57 of the 72 parent couples had always been healthy. In three cases, one of the parents had had rheumatic disease, and in one case typhoid fever, during childhood. The father of one of the lethal cases had had acute poliomyelitis one year before the birth of the child. The mother of one of the lethal cases had had an operation for hyperthyroidism two years before the birth of the child, and had subsequently apparently developed hypothyroidism. The mother of one of the milder cases suffered from a manic-depressive mental disease, and had had electric and insulin shock treatment for a period before the beginning of the pregnancy. In one case the mother had had oophoritis with fever two years before the birth of the child.

The father of one of the milder cases worked as a medical attendant in the X-ray department of a hospital before the birth of the child.

There was otherwise no information which could indicate that any of the parents of the sporadic cases had been subjected to radiation, apart from occasional X-ray examinations.

It may thus be said, in summary, that no basis was found for the concept that maternal age, birth rank, season of conception, place of residence of the parents or climatological conditions, disease in the parents or radiation effects could have had any connection with the occurrence of mutations.

H. Mortality

As shown by the genetic analysis of the familial cases, the disease exhibits a dominant inheritance with almost complete penetrance. It is therefore improbable that a selective mortality occurs in affected children in this group during the first year of life, since an excess mortality before the age at which the disease is diagnosed would give lower values than those obtained by the Mendelian ratio.

It is, however, of interest to investigate even more directly the mortality in different groups of the material. 2 years may probably be set as the age limit before which the disease in the majority of cases may be assumed to be diagnosed.

If, firstly, the mortality before the age of 2 years is investigated in those families in the series, in which the disease occurs in both parents and children, the following is found:

		General population 1941—1950*
Stillborn:	2 out of 297 = 0.7 ± 0.5 %	2.2 %
Died at ages 0—1 yr:	9 out of 295 = 3.1 ± 1.0 %	2.7 %
Died at ages 1—2 yrs:	3 out of 286 = 1.0 ± 0.6 %	0.3 %

* The figures were previously considerably higher

The mortality figures do not differ significantly from those of the general Swedish population, and there is no reasonable cause to suppose that there is a selective mortality in the genotypically affected children with familial occurrence before the age at which it may be assumed that the majority of cases are diagnosed.

In the discussion on Table 5 (p. 40 ff.) which shows the frequency of the disease at different ages in the 1957 Swedish population, it was mentioned that the lower frequency in the higher age groups could possibly be partly due to a higher mortality in these patients. With regard to this question the mortality among the affected familial cases (probands and their affected siblings) was investigated according to the following formula given by Larsson and Sjögren (1954):

$$\lambda = \frac{\Sigma n_d \cdot d + \Sigma n_a \cdot a - \Sigma n_r \cdot r}{\Sigma n_r \cdot e_r - \Sigma n_a \cdot e_a} = \frac{R}{P}$$

where

n_r = the number of individuals coming under observation at the age r;
n_d = the number of individuals dying at the age d;
n_a = the number of individuals still alive on disappearing from observation at the age a;
e_r = the remaining mean expectation of life in the general Swedish population for an individual aged r.

Thus, by means of the formula, for all cases of the disease in the familial material, the number of years that they would have lived under observation if they had had a normal remaining mean expectation of life is calculated, and this sum is compared with the number of years in which the cases examined have actually lived under observation.

In this case the comparison covers the period 1901—1957, during which the mortality in the general population has gradually changed. P has therefore been calculated for different periods, using the appropriate mortality-tables 1901—10, 1911—1920 and so on, whereby, as regards entrances and disappearances from observation, only the conditions from the beginning of the period to its end have been taken into consideration.

A few cases in the material, born during the 19th century, entered under observation at the age which they reached in 1901. Other cases entered at the age of 2 years. The period of observation ends with the age which the individuals reached or should have reached in 1957.

The result of the mortality investigation shows that for both sexes combined the observed number of years survived (R) is 3662, and the expected number of years survived in the general population (P) is 3479, which gives the quotient $R/P = 1.05$. As seen, the value of the

quotient gives no verification that there is any excess mortality among the affected familial cases of osteogenesis imperfecta. The same result is obtained for each sex taken separately.

The above calculations have, as mentioned, only been applied to the mortality among the cases occurring familially. As the sporadic cases, for explicable reasons, are often more severely affected by the disease than the familial cases (see p. 146), it may easily be asked, whether the sporadic cases do not have a higher mortality. An investigation in this respect of the sporadic cases over the age of 2 years, shows that the observed number of years survived is 966, and the expected number of years survived is 926, which gives a quotient of 1.04. No excess mortality after the age of 2 years was thus established in this group.

Different results are obtained, however, if the mortality is calculated on all sporadic cases from birth. This group then also includes sporadic so-called lethal cases. Of 30 sporadic cases in the material, born during the years 1943—1955, 12 had died before the age of 2 years. This gives a frequency of 40 ± 9 %, which implies a significant excess mortality.

In summary, then, it is found in the present material that there is no increased mortality among the familial cases, nor in the sporadic cases after the age of 2 years. On the other hand, there is a significant excess mortality among sporadic cases before the age of 2 years.

J. Fertility

It is of interest, from both the genetic and the socio-medical aspect, to attempt to determine the fertility of individuals with osteogenesis imperfecta.

Of the 190 patients, 65 were men and 57 women of ages 20 years and over. 39 of the men and 34 of the women were married or had been married, and altogether they had 118 children. If the marriage frequency in the different age groups had been the same as in the total Swedish population, it would have been expected that 47 of the men and 46 of the women would have been married, i. e. a total of 93 marriages. As, furthermore, it may be assumed at the present time that somewhat more than 2 children are born for each marriage, approximately 186 children would have been expected in these 93 marriages. If the observed number of children (118) are placed in relation to the

expected number (186), the ratio of 0.63 is obtained, which means that the fertility in this material of osteogenesis imperfecta appears to be about 60 % of that in the general Swedish population.

It is evident that these figures must be taken with some caution. As may be seen from Table 51 in the socio-medical section, the marriage frequency differs greatly in the groups with different degrees of physical handicap, and the relative fertility is therefore influenced by the arrangement of the material with regard to physical handicap. If the milder forms are under-represented in the material the figures obtained are too low. Furthermore, it seems that the low fertility during the first 10—15 years of marriage is to a great part responsible for the low relative fertility (cf. Tables 51 and 52).

K. Estimation of the mutation rate of the gene or genes responsible for osteogenesis imperfecta

When dealing with a dominant genetic disease such as osteogenesis imperfecta, two different methods may be used to estimate the mutation frequency of the gene or genes responsible, namely the direct and the indirect (cf. Mørch 1941, Popham 1953, Neel and Schull 1954, Crowe, Schull and Neel 1956, and Stern 1960).

With the *direct method,* it is presupposed that sporadic cases are due to mutations. The number of sporadic cases born is placed in relation to the total number of births within a certain area during a certain period of time. Since man is diploid and these patients are heterozygotes, the figure obtained is halved, thus giving the actual mutation frequency.

The number of recorded sporadic cases born per 100,000 births during the years 1943—1955 in Sweden, may be read from Table 40. The mutation frequency, $m = 1/2 \cdot 1.94 \cdot 10^{-5} = 0.97 \cdot 10^{-5}$.

With the direct method, the frequency with which the disease occurs sporadically can also be placed in relation to the general frequency of the disease in the population (cf. Crowe, Schull and Neel 1956). As seen in section VI (p. 46), an estimate of the frequency of osteogenesis imperfecta in Sweden gave a most probable figure of $4 \cdot 10^{-5}$, and a maximal figure of $5 \cdot 10^{-5}$. Calculated on all Swedish probands in the whole material (140) (see p. 22), of whom

68 consisted of sporadic cases and with a general frequency of the disease in the population of $4 \cdot 10^{-5}$, $m = 1/2 \cdot \frac{68}{140} \cdot 4 \cdot 10^{-5} = 0.97 \cdot 10^{-5}$ With a general maximal frequency of $5 \cdot 10^{-5}$, it is found in the same way that $m = 1/2 \cdot \frac{68}{140} \cdot 5 \cdot 10^{-5} = 1.2 \cdot 10^{-5}$. Calculated on all Swedish probands alive in 1957 (107 cases), of whom 46 were sporadic cases, with a general frequency of $4 \cdot 10^{-5}$, $m = 1/2 \cdot \frac{46}{107} \cdot 4 \cdot 10^{-5} = 0.86 \cdot 10^{-5}$, and with a general maximal frequency of $5 \cdot 10^{-5}$, $m = 1/2 \cdot \frac{46}{107} \cdot 5 \cdot 10^{-5} = 1.07 \cdot 10^{-5}$.

In the *indirect method* of estimation a stable equilibrium between the mutation rate and the selective disadvantage of the disease is assumed, according to the following formula:

$$m = 1/2 \cdot (1 - f) \cdot R,$$

where

m = the mutation rate per gene per generation;

f = the relative fertility of individuals heterozygous for the particular gene under consideration, so that $(1 - f)$ is the selective disadvantage; and

R = the frequency of the disease in the general population.

The relative fertility *(f)* has been calculated above (p. 162) as 0.63. An estimation of the frequency of the disease (p. 46) has given $R = 4 \cdot 10^{-5}$ as the most probable figure, and $R = 5 \cdot 10^{-5}$ as the maximum figure.

The following mutation frequency is thus obtained:

most probably $m = 1/2 \cdot (1 - 0{,}63) \cdot 4 \cdot 10^{-5} = 0.74 \cdot 10^{-5}$,

and maximally $m = 1/2 \cdot (1 - 0.63) \cdot 5 \cdot 10^{-5} = 0.93 \cdot 10^{-5}$.

The two methods thus give reasonably concordant values for the mutation frequency of osteogenesis imperfecta. According to the calculations carried out, this should lie between $0.7 \cdot 10^{-5}$ and $1.2 \cdot 10^{-5}$.

Only Komai, Kunii and Ozaki (1956) have previously attempted to estimate the mutation frequency in osteogenesis imperfecta. Using approximate figures these authors arrived at a value of $3.95 \cdot 10^{-5}$, thus of about the same order as the values obtained above.

In all mutation rate estimates in man, consideration must be taken of the fact that several factors are subject to uncertainty, and therefore it can be expected that only an approximation will be obtained (cf.

Neel and Schull 1954 and Stern 1960). One of the requirements for the validity of the above calculations, is that the disease is due to a mutation in a single locus. No proof was found in the genetic analysis of the material that this was not so. Under this assumption, the figures obtained can be presumed to give an idea of the size order of the mutation rate of the genetic locus responsible for osteogenesis imperfecta.

L. Linkage study

The linkage relations between blood group markers and osteogenesis imperfecta was studied by means of the sib-pair method. In agreement with a previous study by Mohr (1953) no evidence for linkage was obtained. Nor were there any significant associations between blood groups and osteogenesis imperfecta (cf. Smårs, Beckman and Böök 1961).

Summary of clinical, genetic and epidemiological aspects

The purpose of this study of osteogenesis imperfecta was to broaden the understanding of both the clinical, genetic, epidemiological and socio-medical aspects of the disease.

T e r m i n o l o g y. There are no reasons to distinguish between different types of osteogenesis imperfecta, neither clinically nor histologically. Most observations support Looser's assumption (1906) of o n e disease entity which may appear with various degrees of severity. It does not seem proper to distinguish between osteogenesis imperfecta congenita and tarda, because it may be presumed that all affected have some signs or symptoms of the disease already at birth, and also because the name "congenita" is generally used to indicate non-surviving (i. e. lethal) cases and "tarda" surviving cases. It should, therefore, be more adequate simply to use the terms "non-surviving or lethal cases" and "surviving cases" of osteogenesis imperfecta.

D i a g n o s t i c c r i t e r i a. One of the two main symptoms osseous fragility and blue sclerae are always required for the diagnosis. The other two main symptoms deafness and hyperlaxibility are not critical for the diagnosis. In this work the following diagnostic criteria have been used:

I. For probands:
   1. Blue sclerae and idiopathic brittle bones demonstrated by one or several fractures from inadequate trauma, o r
   2. Idiopathic brittle bones alone, demonstrated by at least 7 fractures not normally justified by the causative force.

II. For secondary cases:
   a) Relatives who fulfil the same criteria as the probands (1 or 2),
   b) Relatives with less severe manifestations such as blue sclerae alone or multiple fractures from inadequate trauma.

Material and methods: The material investigated includes 274 persons with osteogenesis imperfecta in Sweden. Of these 147 were index cases, probands. They were registered through an inquiry in 1956 to all district doctors (cf. footnote, page 19) and most chief physicians of the different hospitals in Sweden. Among the relatives of the probands a further number of 127 secondary cases were discovered. Of the 274 individuals traced, who had the disease, four had emigrated and 80 had died before 1957. Thus 190 individuals could be subjected to a personal examination. Of these 185 were of Swedish and five of foreign birth. A case of foreign birth is defined here as one whose father or mother was not born a Swedish citizen.

The examination of the 190 persons with osteogenesis imperfecta alive in Sweden 1957 was performed as a field investigation, which was thoroughly planned beforehand. A detailed scheme was followed both for the interview and the examination.

It is likely that the registration was practically complete (over 95 %) for those individuals who were diagnosed during the period 1943—1955.

It is conceivable that some such cases, now between the ages of about 40 and 70 years, who 20—50 or more years ago were under 20 years of age, were missed in the reports if they did not belong to the same families as the cases mentioned above.

Another category which may not have been included in the material consists of those individuals in whose families no case of the diseases showed sufficiently obvious signs or symptoms that could lead to a diagnosis.

These suppositions are supported from an analysis of the distribution of the material into age and sex. When compared with the age and sex distribution within the whole population in Sweden it seems likely that there is an underrepresentation in the material of both sexes over 40 years of age and also, to a lesser degree, of females under this age. Probable explanations for this are given.

The frequency of osteogenesis imperfecta in Sweden. An estimation of the frequency of osteogenesis imperfecta in Sweden based on the age and sex distribution of the material as compared with the whole population gave a figure of approximately 300 affected individuals in 1957, i. e. 4 per 100,000.

Disposition of the material. The clinical analysis was based on the 190 surviving cases (osteogenesis imperfecta tarda) who were alive and domiciled in Sweden in 1957, and furthermore on 22

non-surviving cases (so called lethal cases or osteogenesis imperfecta congenita), for whom information was obtained from hospital records and from relatives.

For the genetic and epidemiological analysis those cases whose father or mother were not born as Swedish citizens were excluded from the analysis.

The study of the socio-medical significance of the disease was based exclusively on the 190 individuals who were alive and domiciled in Sweden in 1957. This socio-medical study was carried out in collaboration with R. Berfenstam and will be reported and summarized in a special part after this summary of the clinical, genetic and epidemiological aspects.

Clinical aspects. For the clinical study it is practical to divide the patients into groups of different degrees of severity. Firstly, it is convenient to separate:

1. Non-surviving or lethal cases, named by Looser "osteogenesis imperfecta congenita" and
2. Surviving cases, named by Looser "osteogenesis imperfecta tarda".

The surviving cases are divided according to the degree of impairment of movement:

1. No physical handicap (no difficulty of movement),
2. Slight physical handicap (slight difficulty of movement),
3. Fairly severe physical handicap (great difficulty of movement, but not in need of an invalid chair),
4. Severe physical handicap (invalid chair required).

The majority of the patients had no or only slight impediment of movement (64 % and 17 % resp.), while 19 % of the total material had a more pronounced difficulty of movement.

The main symptoms of the syndrome of osteogenesis imperfecta are osseous fragility, blue sclerae, impaired hearing and hyperlaxibility. Other symptoms which are described in detail are skeletal deformities, a slender body build and small stature, dental changes and a possible tendency to haemorrhagic diathesis. Other symptoms were also noted, but in such a low frequency that they could not safely be correlated with osteogenesis imperfecta.

The liability to fractures varies. The fractures often occur periodically. The majority of the fractures occur in the 2nd and 3rd years of life. The fracture frequency then decreases somewhat, but

at the age of 6—7 years there is again an increased risk, greater for boys than girls, and similarly at 10–15 years, especially pronounced for boys and less certain for girls. From the ages of 15–20 years the fracture frequency is greatly reduced for both men and women. The variation in fracture frequency thus observed at different ages is presumed to be due partly to extrinsic factors such as the varying physical activity and different degrees of caution exercised at different ages, and partly to an intrinsic variation of the bone fragility at different ages. The intrinsic variation may be due partly to endocrinal changes at different stages of development and partly to other endogenous factors. It is possible that some maturation of the defective bone occurs at 15—20 years and that this is partly the reason why a stabilization of the skeleton may be observed at this age. There are some observations indicating the possibility of exacerbating factors, such as pregnancy and lactation, inactivity, and inadequate diet.

Individuals with a large number of fractures have, on the average, a more severe physical handicap. The more severely handicapped have their first fractures before the age of 1–2 years more often than do the less severely handicapped. Of fractures occurring before the age of 2 years, femoral fractures are the most common. This does not mean, however, that an early femoral fracture will in itself, necessarily, cause permanent handicap. It is probable that the occurrence of several fractures at an early age, regardless of locality, indicates a more pronounced osseous fragility with a high risk of permanent damage.

In individuals suffering from osteogenesis imperfecta, fractures of the lower extremities are far more common than those of the upper extremities, while the reverse is found in normal material. An explanation for this is suggested.

A significant association was found between the number of fractures and the number of skeletal deformities in different sites. There is also evidence, however, that the deformities in part may be due to some kind of plasticity of the bone tissue which makes the defective bone yield to the combined strain of body weight and muscle tone. It is believed that most deformities are due to a combined effect of the increased bone fragility and the plasticity of the bone tissue.

The mean body height of individuals with osteogenesis imperfecta is below normal. This is true also for patients without deformities.

Characteristic dental changes were more common in individuals with a severe form of the disease.

The risk of deafness in osteogenesis imperfecta seems to increase steadily up to the age of 50 years. At the age of 40 years about 30 %, and at 60 years about 50 % of the patients suffered from deafness. There was no significant difference in the frequency of deafness between the different handicap groups. Deafness was found in patients with sclerae of normal colour as well as in those with blue sclerotics.

The careful treatment of the fractures is of great importance for the outcome of the disease. There is no reason for a defeatist attitude even if the number of fractures appeares to be endless. The great importance of orthopedic treatment, particularly for the flaccid joints and weakness of the foot ligaments, is also pointed out.

Genetics and epidemiology. In most pedigrees bone fragility occurred together with blue sclerotics in the same individual and in more than one generation. The genetical analysis of these pedigrees showed close agreement with the hypothesis of osteogenesis imperfecta being due, primarily, to a single heterozygous gene difference with complete penetrance. A few other pedigrees, however, indicate that the expressivity of this gene may vary considerably.

In three pedigrees including 7 sibships with a total of 21 individuals all the 9 affected had bone fragility alone. As these affected belonged to different generations it seems unlikely that genetic modifiers could explain the consistent absence of blue sclerotics. It is more likely that the mutations operating in different pedigrees are not always identical, even if occurring at the same locus.

Five sibships with two or more affected members had unaffected parents. It is shown that recessive inheritance is unlikely. The likely explanation is that the effect of the dominant gene may be occasionally completely suppressed.

Only in one family did affected individuals both with or without blue sclerotics occur. This variation could be caused by special genetic or environmental modifiers operating in this family.

The incidence of osteogenesis imperfecta among the children of sporadic cases (i. e. probable new mutations) agrees with the hypothesis that these sporadic cases are essentially genetically similar to the familial cases. Furthermore, sporadic and familial cases showed no significant differences with regard to clinical signs and symptoms.

The sporadic cases were randomly distributed in different birth ranks, and no association with specific maternal age groups was found.

All familial cases and the sporadic cases over 2 years of age displayed no increased mortality. However, the sporadic cases showed significant excess mortality during the first two years of life.

The fertility of affected individuals was estimated at about 60 per cent of normal.

The mutation rate, calculated by the direct as well as by the indirect method was estimated as between 0.7×10^{-5} and 1.2×10^{-5}.

The present data do not support the view that maternal age, birth rank, season of conception, place of residence, climate, parental disease or radiation effects have been associated with the occurrence of new mutations.

The prevalence of osteogenesis imperfecta appears to be the same in different geographical regions in Sweden. However, slightly more affected individuals reside in towns and other built up areas than in sparsely populated areas.

Socio-medical aspects

BY

R. Berfenstam and G. Smårs

A. Introduction

As far as we know no systematic investigation has been previously made on the way individuals affected by osteogenesis imperfecta have managed to adapt themselves to community life. We therefore decided to add to the clinical, genetic and epidemiological investigation a socio-medical analysis.

Since we feel that the report of this study should be accessible to the reader independently of the report presented in the foregoing sections, a short review will be given of some essential characteristics of the disease and the material investigated.

Osteogenesis imperfecta is a rare hereditary disease. The characteristic findings are an abnormal liability to fractures, blue sclerotics, an increased frequency of deafness and in many cases an overextensibility of the joints, called hyperlaxibility. There is evidence that the syndrome is due to a single, dominant, autosomal gene. The majority of fractures occur during childhood. The frequency of the fractures are greatly reduced from 15—20 years of age. In some of the patients the bone fragility results in deformities, mainly of the lower and upper extremities and the spine.

The disease may have any degree of severity. In its severest forms it is incompatible with life; one then speaks of the lethal form or osteogenesis imperfecta congenita. Milder forms are called osteogenesis imperfecta tarda or simply surviving cases.

Material. The present study is based on an investigation of 190 individuals with the disease living in different parts of Sweden in 1957. These persons belong to a material collected by means of an inquiry to all district doctors and most head physicians of the hospitals in Sweden, and by a subsequent field investigation. In 1953—1954, previous to the inquiry, a preliminary inventory was made of individuals with the disease seen in Swedish hospitals

TABLE 41. *Summary of the total material.*

	Total material	Emigrated	Died before 1957	Cases alive in Sweden 1957 = total investigated
Probands	147	1	34	112
Secondary cases	127	3	46	78
Total	274	4	80	190

during the period 1943—1952 (Berfenstam and Smårs 1956). Primarily 147 individuals with the disease were traced by the inquiry (probands). A further 127 cases were found among their relatives; these are called secondary cases. Of all these 274 cases (of whom 22 were lethal) only 190 were found alive in Sweden 1957. (See Table 41.)

The degree of completeness of the collected material was studied in detail previously (see page 33 ff.). It appeared probable that there were altogether about 300 cases of osteogenesis imperfecta alive in Sweden in 1957. The 190 cases examined personally thus constituted about 60 % of the total. It is probable that those cases which were not traced belonged mainly to the following categories: 1) Persons over about 40 years of age, whose active period and the diagnosis of their disease was too far back for them to be reported in the inquiry; 2) individuals in whom the symptoms (in both themselves and their relatives) were too slight for the disease to be diagnosed and reported.

The representativeness of the material was discussed. On the whole, we consider the collected material to be well suited for assessing the clinical variations of the disease, and also for using it as a basis for a socio-medical study (cf. pp. 43—44).

Interview and examination. The personal interview of the patients was carried out according to a questionnaire, prepared in full detail before the field investigation, including questions concerning personal data, family conditions, and the disease history of the patient. An interview was made to assess the effect of the disease on the general living conditions of the patient. The examination was performed as a general physical examination. The healthy relatives were interviewed and examined, but less extensively.

The extent of the socio-medical interview may be seen by the summary of the questionnaire (page 25). With a few exceptions, the interviews and examinations were carried out in the patients' homes.

Classification of the material. For the socio-medical as for the clinical analysis of the material, it was found convenient to divide the 190 individuals examined (all of whom were of the type osteogenesis imperfecta tarda, surviving cases)

into four groups, according to physical handicap, i. e. to the degree of impairment of movement:

1. No physical handicap (= no difficulty in movement)
2. Slight physical handicap (= slight difficulty in movement)
3. Fairly severe physical handicap (= much difficulty in movement but not in need of an invalid chair)
4. Severe physical handicap (= invalid chair required).

In evaluating the degree of movement handicap for this classification, attention was paid mainly to the ability to move about but also to some extent to the ability to use the arms, particularly with respect to manual dexterity.

B. The suitability of the material for a socio-medical study; some considerations of disabling diseases

It seems fairly evident that osteogenesis imperfecta has a lengthy course, and in general presents the picture of a long-term disease with more or less severe functional reduction.

In order to study how patients with osteogenesis imperfecta adapt themselves as members of a community, it seemed useful to survey the literature relating to patients with other chronic diseases, and the means taken to facilitate their adaptation. This survey has been limited as far as possible to diseases with impediment to movement, to which class, functionally, osteogenesis imperfecta most closely belongs.

We have attempted to obtain data about the following problems:

1. The order of magnitude of the social and economic aspects of chronic diseases, especially those with movement hindrance, which are primarily represented by the rheumatic diseases.
2. The meaning of the terms "ability to work", "partial working ability" and "disablement".
3. Other possible factors of significance, apart from the defect in anatomical function.

Kahlmeter (1923, 1932) was one of the first authors to draw attention to the very large social and national economic significance of the chronic diseases. He pointed out the dominant role of the rheumatic diseases as a cause of persistent loss of working ability. No other chronic disease group, except perhaps tuberculosis, has been the subject of such detailed socio-medical studies as the rheumatic diseases. Some figures from Edström's investigation in 1943—44 give an idea of the social and economic significance of the rheumatic diseases in Sweden; these figures still seem to be valid when compared with those of more recent investigations (Inghe 1958, Bjure 1958). Edström estimated that, in 1943—44, 42.000 persons out of 130.000 with active rheumatic disease were

rheumatic invalids, and at the same time about 80.000 persons daily were disabled because of the disease. There is no exact information for Sweden, about the number of cases of non-rheumatic diseases who are fully or partially disabled. We know that owing to disablement for various reasons approximately 127.000 (2.6 %) of the population aged 16—66 years were receiving invalid pensions on January 1, 1957.

The concept of "working ability" and "partial working ability" is clarified by a statement made by the Committee for the Partially Disabled (Kommitténs för partiellt arbetsföra betänkande I, 1946), which helps to define these terms.

The Committee points out the following: "The borderlines between those fully capable of working, the partially disabled and the completely disabled are indistinct. The actual degree of working ability is to no low extent dependent on what type of work is used as a basis for the assessment. As is often pointed out in discussing this question, strictly speaking all individuals are partially unable to work, in the sense that they could not support themselves in every type of work, but only in a certain number of the different occupations which are to be found in the community. There are many who must be regarded as partially unable to work in certain types of heavy occupations, such as forestry, building labour, etc., without being considered at all disabled for other occupations, where they can achieve full efficiency. On the other hand there is almost always some sort of work, which can be carried out even by persons with very obvious disablement. — — Provided that a person classified as partially disabled obtains suitable work, his general working incapacity can be eliminated, and he need not subsequently be regarded as partially disabled within his new occupational area. Regarded from this aspect not even highly graded invalid persons need to be denoted as partially disabled, if they procure work of such a type that their disablement no longer causes immediate obstruction to the performance of their duties."

The Committee stated the following, as a definition of the term "partially disabled": Partially disabled persons are those, "who by reason of physical or psychical hindrance to work, or social handicap, have or may be expected to have more difficulty than others in obtaining and retaining work".

The question of a possible correlation between anatomical defects in function and social adaptation in the rheumatic diseases does not seem to have been studied in great detail. This question, however, has been discussed in relation to studies on individuals receiving social relief. It has also been treated to a certain extent in modern rehabilitation discussions, since in all rehabilitation work the reduction in function must be weighed against other factors.

Regarding the incidence of different diseases in persons receiving social relief, it is often difficult to decide whether it is the physical, psychical or social factor which in any particular disabled person has the greatest significance for the reduced working capacity (cf. A. Rülcker 1942, Teilmann 1954 and Inghe 1958). Teilmann states, for example, that he often found a case where physically the disease was not of any vital importance as regarded the need for assistance, but after discussion with psychiatrists, social authorities, and sometimes

psychologists, it would be clear that because of the social circumstances and psychological situations at that particular time, help was nevertheless required.

In the extensive literature dealing with modern rehabilitation, we have selected only two authors, Ruesch and Alvarez, who treat the rehabilitation problem in its broader aspects, and two others who give special attention to diseases with impediment of movement (Lowman and Rusk).

In an article entitled "Mastery of long-term illness", J. Ruesch (1949) says: "One can say definitely that if a person is afflicted with a disease and continues to live, restoration to health depends upon whether or not bodily, psychological and social function can be utilized for an integrated response. If such is the case, further psychological and social growth is likely in spite of disease or invalidism, and the person can be considered to be healthy".

Alvarez (1949) indicates as two main points in the treatment of the chronic sick, that firstly, there should be as good and as comprehensive a diagnosis of the condition as possible, and secondly, an attempt should be made to teach the patient to live with his handicap and to adjust his life in the best possible way in the community.

A report made by Lowman (1955) of the program which he followed in the rehabilitation of patients with rheumatoid arthritis, may be used as an example of how modern rehabilitation of persons with impairment of movement is carried out in detail. If necessary the basic general examination was complemented by special investigations. Special functions were then analyzed, such as muscle strength, joint movement, the ability to carry out certain movements in daily life, e. g. eating, dressing etc. Finally, an attempt was made to assess the psychical, social and economic prospects in each case, and form an idea of the patients' own desires and disposition as regards occupation and future plans. These latter factors were considered just as important for successful rehabilitation as any of the more obvious medical aspects.

Guided by all the data collected, an individual plan for each of the patients was made. While the treatment was in progress the development of each patient was observed, and, when desirable, the plan and aim of the rehabilitation was re-evaluated. The treatment consisted of special medical, physical and occupational therapy, training of special functions, psychological and psychiatric help, advice in choice of occupation, and, when necessary, occupational training.

By means of this program, an obvious improvement in movement was attained in all cases, and a number of patients were able eventually to begin full time work.

Good results may also be obtained in patients disabled because of severe chronic neurological diseases by building up a program of physical medicine rehabilitation on the basis of the personal interests and remaining functions of these patients, as shown by Rusk (1949).

Of the large group of people with chronic diseases, those cases suffering from osteogenesis imperfecta constitute only a very small part.

It is noteworthy, that although many authors, even in the last 20--30 years, have described the disease, the socio-medical aspects have in general received little attention. Seedorff (1949), however, mentions certain social aspects, and points out that the patients often show considerable power of initiative, and in many cases succeed in adapting themselves and finding suitable work and a good position in the community. He also points out their desire to support themselves as far as possible. Seedorff, however, gives only individual examples, but no detailed analysis.

As will be discussed in a later section, and as pointed out by Seedorff, the impression is obtained that there is a special power of initiative, or "drive", in many of these often severely affected people, which prevents them from allowing the disease to become too great a burden, and more often spurs them on to make the best possible of the situation. The impression is also obtained that these affected people often make good use of their intellect, and in many cases have been able to progress in independent and more intellectual occupations.

It is often difficult to assess an individual's possibilities of adaptation to a community merely on the basis of a given diagnosis or from a functional reduction of a defined anatomical defect. This is an observation often made by physicians as well as others engaged in social work. Other factors often play a decisive part.

One of the most important of these factors is the intellectual capacity; of others may be mentioned the way in which the affected person learns to accept his handicap and live with his disease, the attitude of the family and community, the patient's own ability and the resources of the community from the training and occupational point of view to utilize those powers of the handicapped person which could compensate for his disability.

Our cases of osteogenesis imperfecta, who as regards functional reduction are extremely variable but who are well demarcated and easy to survey, should be particularly suitable for a study of such problems.

During the investigation of the patients, individuals were repeatedly encountered, who spontaneously led one's thoughts to this problem. One such case was a 28-year old man with extremely severe functional disability, who in spite of this had obtained a good economic position, not only supported himself but also helped his parents, and was also well adapted to the life of the community.

Even if, socially and economically, osteogenesis imperfecta does not create any great problem to the community, it is nevertheless of especial interest from the socio-medical aspect, in that it may be said to constitute a prototype of an early developed, disabling disease, and also of a hereditary disease which has the somewhat rare property that it is almost a pure physical disease. In osteogenesis imperfecta a psychical insufficiency state or defect appears to be no more frequent than in the average population.

It therefore seems advantageous to utilize this relatively well demarcated material for a careful socio-medical study, with especial regard to the problems discussed above.

We should have liked to compare this material with that of other diseases, in which a reduction in function of one kind or another is a prominent feature; unfortunately no material suitable for comparison was found.

C. Review of the distribution of the material with regard to degree of physical handicap, age and sex and place of residence

In order to discuss the Swedish material of osteogenesis imperfecta from a socio-medical aspect, a short review of some aspects will be given below.

It has been mentioned previously that the material consists of 190 surviving cases. A distribution based on the degree of physical handicap in respect to impairment of movement, is given in Table 6. The majority (81 %) have no or only slight physical handicap (64 % and 17 % respectively). Only 19 % of the total have a more pronounced movement handicap.

The distribution based on age and sex may be seen in Table 4 (p. 40), which for comparison also gives the corresponding frequency figures for the whole population in 1957. The deviations from the cor-

responding distribution in the whole population, which may be observed, are discussed in more detail in the account of the material (p. 40 ff.).

The place of residence in 1957 of the 190 cases investigated is given on the map in Fig. 3. The distribution mainly follows the map of the general population (cf. The geographical distribution of the disease, p. 153 ff.).

The distribution of the cases into towns, other built up areas and sparsely populated areas may be seen in Table 42, which also gives the corresponding distribution for the whole population in the census of 1950. We have, in principle, attempted to apply here the definition of other built up areas taken from the census of 1950, i. e. densely populated places with over 200 inhabitants, and sparsely populated areas as those with less than 200 inhabitants. It may be seen in the table that osteogenesis imperfecta when compared with the whole population is somewhat overrepresented in towns and other built up areas and somewhat underrepresented in sparsely populated areas. This is probably at

TABLE 42. *Distribution of the material by residence in towns, other built-up areas (with more than 200 inhabitants) and sparsely populated areas.*

Degree of handicap	Age (years)	Towns	Other built-up areas	Sparsely populated areas	Total
None and slight	1—24	34	19	13	66
	25—	52	20	16	88
	Total	86	39	29	154
Fairly severe and severe	1—24	6	5	5	16
	25—	11	4	5	20
	Total	17	9	10	36
Total material	1—24	40	24	18	82
	25—	63	24	21	108
	Total No	103	48	39	190
	%	54.2	25.3	20.5	100
Census Dec. 31, 1950; %		45.6	20.6	33.8	100

least partly associated with the fact (see Table 55) that this group of individuals is underrepresented in the heavier occupations connected with agricultural work and its ancillary industries, which predominate in sparsely populated areas, while they are overrepresented in the lighter occupations associated with trade and other related occupational groups, which to a great extent are to be found in towns and other built up areas. Another probable contributory reason for the fact that these individuals appear to prefer towns and other built up areas, is because it is easier to obtain help and care there.

It was mentioned above that the majority of the patients have no or only slight physical handicap in regard to mobility. This means that a large number of those suffering from the disease are well able to adapt to community life. It must be remembered, however, that the majority encounter some difficulties by reason of the disease; there are repeated visits to the doctor and hospital treatment, interruptions in school attendance and at work, as well as problems concerning choice of occupation and in many other respects. The degree to which the disease influences the formation of families is also a question of importance.

D. The burden placed by the disease on the local health services

It is reasonable that a disease with manifestations so alarming as fractures of various kinds, becomes to a considerable extent the object of attention from the medical services. In the past, as far as can be judged, the fractures were allowed to heal as well as possible without any special therapeutic measures. The present attitude, however, demands more active care in order to reduce the risks of bad positioning and other post-fracture deformities. The contributions for those affected in such an acute stage are certainly well worth making.

During the active periods of the disease, a number of cases need prolonged hospital care, and everything supports the view that in such cases extended care in hospital constitutes an important requirement for the best possible restitution of function, and is therefore rewarding in the long view.

In addition to the medical care during the acute stage, medical rehabilitation is certainly of great importance in these cases. The extent to which rehabilitatory treatment is exploited by this group of affected individuals is discussed later (page 201).

In attempting to find some way of estimating the contributions made by the medical services for these cases, we have for practical reasons directed our attention to points about which information is easily available, but which give some idea of the problem. With this limited aim, we have restricted ourselves to the following questions:

1. The total number of fractures for osteogenesis imperfecta patients of different age groups and different groups of physical handicap.
2. The total length of time spent by these patients in hospital by reason of the disease.
3. The total number of visits to doctors, for the disease.
4. The total distance travelled by medical transport (car or ambulance) for these patients on account of the disease.

The information obtained was that recollected by the patients, complemented as far as possible with the help of hospital records. Thus, in general, some underestimates can be expected.

Since the information from the older age classes appears to be less adequate, only that for ages up to 30 years is reported here. The fact that the information was found to be rather lacking from the older age groups is probably partly due to greater difficulty in remembering fractures and hospital visits from a long time ago. It may also be due to the fact that in previous years people were less inclined to seek medical care, especially for such a disease in which a fracture appeared to be a more or less common occurrence, and where the impression was obtained that nothing could be done about it. Further, in previous years the medical services were not so well developed, either for diagnosis or treatment.

Many of these patients have had a surprising number of fractures, often at a site which to a great degree has jeopardized function. Some have had over 50 fractures. In general, men had a greater number than women. Since the total number of fractures is related to age, the mean number of fractures for different age groups is given in Table 43.

The best idea of the direct costs paid by the community for this disease is probably obtained by means of the information regarding the total length of time spent by these patients in hospital.

TABLE 43. *Mean number of fractures in cases of osteogenesis imperfecta with and without physical handicap in different age groups. (Both sexes)*

Age at examination	Without physical handicap		With physical handicap		Total	
	No. of individ.	Mean No. of fractures	No. of individ.	Mean No. of fractures	No. of individ.	Mean No. of fractures
1— 4	6	2.5	1	(4.0)	7	2.7
5—14	27	5.9	12	16.5	39	9.2
15—29	31	5.9	20	25.8	51	13.7

TABLE 44. *Mean number of days spent in hospital because of osteogenesis imperfecta by patients with and without physical handicap. (Both sexes.)*

Age at examination (years)	Without physical handicap		With physical handicap		All cases	
	No. of individ.	Mean No. of days	No. of individ.	Mean No. of days	No. of individ.	Mean No. of days
1—4	6	26	1	(21)	7	25
5—14	27	31	10	716	37	216
15—29	30	68	19	1,201	49	507

TABLE 45. *Mean number of medical attendences for osteogenesis imperfecta by patients of different ages with and without physical handicap. (Both sexes.)*

Age at examination 1957	Without physical handicap		With physical handicap		Total	
	No. of patients	Mean No. of med. attend.	No. of patients	Mean No. of med. attend.	No. of patients	Mean No. of med. attend.
1—4	6	6	—	—	6	6
5—14	27	17	9	40	36	23
15—29	27	15	17	56	44	31

TABLE 46. *Mean number of kilometers travelled by patients by car or ambulance, for medical attendences because of osteogenesis imperfecta.*

Age at examination	Without physical handicap		With physical handicap		All cases	
	No. of patients	Mean No. of kilometers	No. of patients	Mean No. of kilometers	No. of patients	Mean No. of kilometers
1—4	6	173	—	—	6	173
5—14	25	537	9	879	34	627
15—29	23	287	16	2,100	39	1,031

As may be seen in Table 44, the duration of hospital care is on an average long. For the 93 patients under 30 years of age, the mean time of hospital care during the last 30 years was 365 days. This would mean, that of this small group of affected individuals, during the 30 year period up until 1957, an average of three of the country's hospital beds have been continuously occupied by osteogenesis imperfecta patients who were in 1957 under 30 years of age. The women in the material have spent a significantly shorter time in hospital than the men.

Some concept of what the disease has further cost to these individuals may be obtained by calculating the total number of medical consultations made by those patients who at the time of the investigation were under 30 years of age, and also the total distance in kilometres for which they have had to utilize medical transport for reasons of osteogenesis imperfecta.

As may be seen in Tables 45 and 46, the mean number of such medical consultations for those who, in 1957, were between the ages of 15 and 29 years was 31, and the mean number of kilometres for medical transport was 1,031 per patient. It must be remembered that for several reasons we are concerned here with minimal values. Several of the most severe cases have thus had to be excluded, because they could not give even approximate figures. They could only state that they had visited doctors and used hospital transport for fractures "countless times". In other severe cases, visits to and consultations with doctors occurred only during shorter periods; the most active stages of the disease were spent more or less permanently in hospital.

The advantages offered, even to the chronically ill, by the new sickness insurance, must have been a tremendous boon to these patients.

Under the present rules every such patient, whether or not he is pensioned early, obtains, in case of illness, medical care and travel contribution, and also hospital treatment up to 2 years for each disease before pensioning and up to 180 days for those receiving pension. After this period he pays approximately 5 Sw. cr. daily for hospital treatment.

E. School attendance, school gymnastics and military service

1. General school attendance

Attendance at school is important in relation to later adaption to life, and it is therefore of interest to ascertain how it has been affected in this group of patients. Since the clinical study of the material reveals that the disease is usually most active during the growth period, it might be expected that school attendance would thus suffer considerably. It is also of value in assessing the physical ability, to find out the extent to which school gymnastics and military service could be performed.

Since the educational system has undergone great changes during the period covered by this survey (ages from 2 to 82 years), it has been considered more convenient to limit the assessment of school attendance and gymnastics to the years in which conditions were somewhat similar. The ages from 8 to 39 years were therefore chosen, i. e. persons who attended school after 1923.

The extent to which different age groups (ages 8—39 years), classified according to different degrees of movement handicap, were able to attend normal classes at a primary school, or were in need of other forms of education, may be seen in Table 47; the table shows, further, the number who attended school after both primary and secondary school. There is no apparent sex difference in this respect, and the figures are given for both sexes combined.

Regarding primary school education, it was found that of the patients without handicap, all were able to attend a normal class, except two, who for reasons other than osteogenesis imperfecta were taught in special classes. Two of the

TABLE 47. *Types of education received by patients with osteogenesis imperfecta aged 8—39 years. (Both sexes.)*

Type of school		No handicap (71 cases)		Slight handicap (14 cases)		Fairly severe and severe handicap (24 cases)		All cases (109)	
		No.	%	No.	%	No.	%	No.	%
Primary school	Ordinary schools	69	97.2	12	85.7	5	20.8	86	78.9
	Other forms of education	2	2.8	2	14.3	19	79.2	23	21.1
Education beyond primary level		20	28.2	4	28.6	4	16.7	28	25.7
Education beyond the lower certificate examination (real examen)		1	1.4	—	—	1	4.2	2	1.8

patients with slight handicap, on the other hand, were prevented from attending an ordinary primary school because of their fractures; one was educated at a boarding school attached to an institution for the disabled, and the other only attended school for one year, receiving the rest of his education at home; this was partly due to repeated moves between Sweden and Finland.

Of those who were fairly severely handicapped (8 men and 4 women), only 2 attended an ordinary primary school, 6 received the whole of their primary school education at a boarding school at an institution for the disabled, 3 were taught by teachers at the patients' homes, and one was taught partly at home and partly (for 2 years) at a boarding school for the handicapped. Of especial interest in this group are the two patients who attended an ordinary primary school. One of them, a man, who was 39 years old at the time of the investigation, was transported to school in a wheel chair, often helped by school friends, and crept on all fours into the schoolroom. The other, a 31 year old woman, for 6 years was taken 2 km. either by bicycle or car to a primary school. For the 7th primary school year she attended a boarding school.

The majority (six patients) of the most severely affected, wheel chair cases, also received their primary school education at a boarding school for the handicapped; for two of them the teacher came to their homes, and one attended a nearby primary school for three terms, taken there by his relatives. He was subsequently self-taught. Three patients went to an ordinary primary school. One of these was pushed in an invalid chair by his mother for 3 km. to and from school. The family could not afford to use a taxi except on isolated occa-

sions. A taxi cost about 5 crowns in one direction only, and the family received only 3 crowns per day in repayment for school transport. Another travelled to school on a tricycle, and crept into the schoolroom. For half of the 7th school year the patient attended a boarding school. The third, a woman, had almost completed her school years before the onset of the disease.

It is thus fairly clear that in the age groups discussed, all of the patients received satisfactory education in one way or another. When attendance at an ordinary primary school was not possible, other schools or methods of education were used. Whatever form of schooling was used, however, bone fragility and the complications associated with it interrupted school attendance to some extent in the majority of cases. In the group without handicap, however, the fractures were as a rule of such a type that they healed without complications, and these patients were not hindered to any great extent from attending school; but in the groups with handicap, fractures and other complications required longer periods of treatment, and this prevented school attendance from periods varying from months to even years. This occurred up to the age of 15 years (i. e. before the end of school age) in 57 % of the slightly handicapped cases, and in 71 % of the cases with fairly severe and severe handicap to movement.

Studies after the age of 15 years were also interrupted in a similar way.

2. Education above the primary level

It may be seen in Table 48 that in all, 37 of the total of 151 persons in this material born before 1943 received some school education beyond the primary school stage. The values for men and women have been combined, since no differences between the sexes have been found. As regards less advanced secondary education, 1—3 years of higher elementary school or trade school have been included, and also equivalent education and part of the intermediate school, when school attendance had been discontinued or not yet completed at the time of the investigation.

To compare the frequency of school attendance above the primary level in this osteogenesis imperfecta material with corresponding indi-

ABLE 48. *Percentage distribution based on degree of education of males and females with osteogenesis imperfecta, 14 years of age and older, grouped after year of birth.*

Level of education	Year of birth									
	before 1908		1908—1929		1930—1939		1940—1943		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
rimary school	36	94.7	*45	76.3	22	66.7	11	52.4	114	75.5
igher elementary school and part of intermediate school and similar	1	2.6	6	10.2	3	9.1	10	47.6	20	13.2
ower certificate examination (real examen)	—	—	4	6.8	8	24.2	—	—	12	7.9
igher certificate examination (studentexamen)	1	2.6	2	3.4	—	—	—	—	3	2.0
niversity	—	—	2	3.4	—	—	—	—	2	1.3
Total	38	100	59	100	33	100	21	100	151	100

* Of these 2 patients, who learned reading and writing from their parents and siblings.

viduals in the general population, it is most convenient to select those who passed the lower certificate examination during the 10-year period 1946—55. In the osteogenesis imperfecta material this corresponds to the group born between 1930 and 1939. During this period 12.5 % of the young people in Sweden passed this examination (no sex variation). In our series of cases, 5 out of 20 boys and 3 out of 13 girls passed this examination, i. e. 24 %. These figures are thus double those for the frequency in the general population, but the material is too small to estimate with certainty whether this increase in frequency is real. This is highly probable, however, and the fact that out of 21 children of ages 14—17 years no fewer than 6 (i. e. 29 %) were attending intermediate school at the time of the investigation, provides further support for this contention. Even if no definite figures are available for comparison with the general population for 1957, 29 % appears to be high.

3. School transport

Regulations regarding State grants for school transport have been found since 1926 for those children whose homes were a long distance (3 km or more) from the school. From an original 50 %, the grant was increased in 1935 to 80 %. The other 20 % is to be paid from the local community. In exceptional cases, however, more than 3.25 or 3 crowns can be paid, which constitutes the daily State subsidy for board and lodging accommodation in a private home or student home respectively. In the directions of the Board of Education (Skolöverstyrelsen) of the Ist March 1950, it was stated that "if the conveyance is intended to transport children who are certified by a medical certificate as 'delicate', State aid should be granted, even if the distance to school is less than the minimal distance required in normal cases". According to the regulations for primary schools (of May 23, 1958, chapt. 2, par. 17), different educational arrangements shall be made for pupils who for some reason or other have difficulty in taking part in the usual school instruction.

School transport would have been of great advantage for at least four of the cases described previously. It would have been especially desirable in the case of two, who lived at a distance of 2 and 3 km. respectively from school, if a larger grant for school transport could have been obtained. One of these cases attended school after 1950, when the instructions of the Board of Education came into force.

Each case is, of course, assessed on its own merits as to whether the community should pay for school transport, or the fee for private education or boarding school. It should be remembered, however, that it can hardly be more costly to arrange transport to and from school than to provide for boarding school education, even if the present maximum daily grant were to be substantially increased. Moreover, it is probably better for these children, as for others, to be able to live at home.

4. School gymnastics and military service

Because of the variations in school gymnastics, even for age groups attending school after 1923, the question of the extent to which the children took part has been difficult to assess. Ability to do school gymnastics has been considered to exist, when the child took part in the program arranged, with no or only little restriction.

As shown in Table 49, more than 2/3 of the patients without handicap, and 1/3 of those with slight handicap, took part in school gymnastics. Of the more severely affected, none took part, except for one who had no symptoms until the age of 12 years.

TABLE 49. *Patients (8—39 years of age) with osteogenesis imperfecta, who have participated in school gymnastics. (Both sexes.)*

Degree of handicap	Total	Participated in school gymnastics	
		No.	%
None	71	50	70.4
Slight	14	5	35.7
Fairly severe and severe	24	1	4.2

TABLE 50. *Men over 20 years of age with osteogenesis imperfecta and different degrees of handicap, who have carried out military service.*

Degree of handicap	Total No. over 20 years of age	No. of whom carried out military service	
		No.	%
None	39	23	59.0
Slight	12	3	25.0
Fairly severe and severe	14	—	—

Somewhat the same situation is shown in Table 50, regarding the performance of military duties. Of the 23 who were not handicapped, and who carried out these duties, 10 (possibly 12) were denoted as fully fit for military service, groups I—III, 7 were given more sedentary duties (due to fractures, crooked elbows, flat foot, weak back), two were placed in group III with light duties because of small stature, and two in sedentary duties for other reasons. 16 individuals were exempt from military service for approximately the same reasons as those mentioned above for the others. The three slightly handicapped cases who carried out military service could probably be denoted as being without handicap during the military service age.

It was obvious in many cases, that the patients rather sought to conceal their bone fragility in order to be accepted for military service, than to attempt to exploit their disease in order to be exempted, which would have been justified in the majority of cases.

F. Family data

1. Marriage frequency

The marriage frequency in our series for the age groups between 20 and 69 years is shown in Table 51. While for the non-handicapped this is almost as high as for the average population, it decreases, as expected, with increasing disablement. The frequency of the total (59.5 %) is therefore lower than for the entire population.

No marked differences between the sexes were found in this material as regards marriage frequency, and figures for the two sexes combined are therefore given.

2. Number of children

In order to obtain some idea of the fertility in this material of osteogenesis imperfecta, a calculation has been made of the mean number of children per marriage in patients alive in 1957 with no or only slight impediment to movement. Individuals with fairly severe or severe im-

TABLE 51. *Marriage frequency among men and women with osteogenesis imperfecta with different degree of physical handicap in different ages, compared with the general population in Sweden 1957.*

Age (years)	No handicap		Slight handicap		Fairly severe and severe handicap		All cases			Percentage married in the general population 1957
								Married		
	Total	Married	Total	Married	Total	Married	Total	No.	%	
20—29	18	6	3	1	8	1	29	8	27.6	49.5
30—49	37	31	7	4	12	3	56	38	67.9	84.3
50—69	20	17	12	9	4	—	36	26	72.2	83.3
Total No.	75	54	22	14	24	4	121	72	59.5	
% married	72.0		63.6		16.7		59.5			77.2

pediment to movement have not been included, as in this respect they are in an exceptional position; this group is too small to be analyzed alone. Of all the 24 individuals over 20 years of age in this group, four were married and one had one child.

As pointed out in the population census of 1930 (concerning the number of children in a family — an analysis according to the duration of a marriage and the wife's age at the time of marriage), the mean number of children per marriage is a concept with varying significance. The marriages in question here, like those of the series subjected to analysis in the censuses of 1930 and 1935/36, took place at very different periods, the oldest several decades before the investigation, and some as recently as during the year of investigation. Consequently, a period with very varying general birth rates is concerned here. The material was too small for division into groups according to the age of the wife at time of marriage.

As distinct from the material used for the population census, marriages dissolved because of the death of one of the partners (6 cases) or by divorce (3 cases) have been included in this study. This should not, however, reduce the validity of a comparison with the census material to any great extent. The considerable decrease in the birth rate between the time of the census and this investigation must, however, be of great significance. With these reservations, our series of cases appear to be otherwise comparable with those of the censuses.

As shown in Table 52, the figures of the osteogenesis imperfecta material for the mean number of children are lower than the corresponding figures from the censuses of 1930 and 1935/36. This should, however, be regarded in the light of the continued reduction in fertility which has taken place since the time of these censuses, and which was illustrated in Quensel's (1945) population forecasts (see Table 53).

It is, then, more desirable to compare the mean number of children in this material with those figures given as the calculated number of children in Table 53 for later years up to 1955.

There is thus reason to presume that the mean number of children of the marriages among these cases of osteogenesis imperfecta, excluding the more severely handicapped, is on the whole only a little less than that of the total population during the corresponding period.

There seems to be a lower mean number of children, however, in marriages of patients who were 20—29 years of age at the time of the investigation. It is probable that this generation, more so than the

TABLE 52. *Marriages and number of children among patients with osteogenesis imperfecta (excl. cases with fairly severe and severe physical handicap). (Both sexes.)*

Duration of marriage, years	No. of marriages			Total number of children		
	With children	Without children	All marriages	No.	Mean number of children in marriages with children	Mean number of children in all marriages
— 5	4	5	9	5	1.25	0.56
5—10	4	2	6	4	1.00	0.67
10—15	12	4	16	21	1.75	1.31
15—20	12	—	12	28	2.33	2.33
20—25	9	—	9	24	2.67	2.67
25—	14	4	18	33	2.36	1.83
All marriages	55	15	70	115	2.09	1.64
Mean number of children at census 1930					3.80	3.28
Mean number of children at census 1935/36					2.87	2.29

TABLE 53. *Calculated mean number of children in unbroken marriages of different duration in the years 1940—1960 in the general population (Quensel 1945).*

Duration of marriages	Mean number of children per marriage 1935	Calculated mean number of children in marriages 31 st Dec.,				
		1940	1945	1950	1955	1960
0— 5	0.77	0.68	0.80	0.82	0.85	0.87
5—10	1.51	1.40	1.53	1.66	1.68	1.74
10—15	2.12	1.86	1.88	2.00	2.13	2.16
15—20	2.74	2.31	2.11	2.13	2.23	2.35
20—25	3.29	2.80	2.39	2.20	2.24	2.38

previous ones, has paid more regard to the risk of transmitting the disease to the offspring and that this has resulted in a smaller number of children in these marriages.

G. Aspects of abortion and sterilization in osteogenesis imperfecta

Eugenic indications for abortion and sterilization were established by the law of 1938 (amended 1946) regarding the discontinuation of pregnancy, and by the law of 1941 regarding sterilization. It is stated in this law, that pregnancy may be discontinued, or sterilization carried out, when it can be presumed with good reason that the child by inheritance will be insane, feeble-minded, or severely handicapped by a serious disease or malformation. When the woman is the carrier of such hereditary factors, she must generally undergo sterilization at the time of the abortion.

There has probably always been a desire among people with a sense of responsibility, that severe hereditary diseases should not be transmitted to the coming generations. Ekman, for example, in his dissertation of 1788, described the terrible deformities exhibited by three generations of one family, and ended the description of Anna, the only remaining member of the family, with the words "we hope that this family of poor cripples will die out with her".

With the increased possibilities of legal abortion and sterilization in Sweden, and increased knowledge on these subjects among the population, it follows that patients who suffer from osteogenesis imperfecta and know the hereditary nature of the disease, will probably be aware of the possibilities of limiting the number of children and preventing children with the disease from being born.

Since it is found that the fertility in these cases, regarded as a whole group, is not much lower than that in the average population, it is natural that the problem often arises. During the field investigation and the study of these cases, three patients, during the course of 1½ years in 1957—58, asked us directly to what extent eugenic indications for abortion could be considered.

According to available information from the Medical Board, three abortions on eugenic grounds were carried out during 1950—1957 be-

cause of osteogenesis imperfecta. There were, in 1950, one case on eugenic indications for the woman, and in 1957 two cases, because of osteogenesis imperfecta in the man and the woman respectively.

No recorded cases of sterilization were found for this period, although it might have been expected, according to the law, that sterilization was performed in the two of the above-mentioned cases, where the woman was the affected partner.

The heredity in osteogenesis imperfecta can be generally said to follow the rule of simple dominance, the risk that an expected child contracts the disease being therefore 50 %, when one of the parents has the disease (see genetic analysis).

The question of whether or not osteogenesis imperfecta is to be regarded as a severe physical disease, is less clear. It seems clear that for a number of cases with severe deformities and severe physical handicap, the answer should be an unequivocal "yes". For other cases with few or no deformities and little or no handicap (and such cases are in the majority), the answer should be "no" — assuming that the degree of severity of the disease does not vary from one generation to another.

This assumption cannot, however, be taken for granted. Some illustration of this question may be obtained from the genetic analysis of the present series of cases.

Of the different families in this material, it was possible to examine 31 with cases of osteogenesis imperfecta in two or more generations. When these families were studied with the aim of finding out how the degree of severity of the disease, assessed according to physical handicap (cf. p. 150), varied within these families, especially from generation to generation, the following was found:

1. In 17 families the character of the disease remained unchanged at a constant degree of severity, both within each generation and from one generation to another.

2. In 12 families the physical handicap varied within two near degrees of severity. In 8 of these the subsequent generations kept within the same handicap groups as the previous generation, or exhibited somewhat milder forms. In 4 families a change towards the next more severe degree of handicap was observed in a later generation.

3. In 4 families, varying degrees of physical handicap occurred, spread over three degrees of severity, and in three of these families one

case was found in a later generation with more than one degree more severe handicap than had occurred in previous generations.

To judge by the findings in these families, it appears that the degree of severity of the disease remains for the most part rather similar within any one family, and that children of parents with osteogenesis imperfecta contract the disease in approximately the same degree of severity as the parents, when they inherit the abnormal gene. There is, however, some possibility of a change in the degree of severity to the nearest milder or more severe handicap group. Only in exceptional cases (in this series 3 out of 131 cases = 2.3 %) does the severity increase more than one degree (measured by degree of handicap) in a succeeding generation.

This applies to cases belonging to the families with osteogenesis imperfecta in several generations, where the disease occurs as a rule in one of the milder forms. Individuals with the most severe degree of handicap were not found in these families, only among the solitary cases, and in three of the families in which several children had osteogenesis imperfecta although the parents showed no evidence of the disease. There is, however, reason to suppose that the rule regarding the retention of the degree of severity from one generation to another also holds if a patient with osteogenesis imperfecta tarda in this severe form reproduces. Illustrating examples are found in the literature. In the family described by Ekman in 1788, several generations exhibited pronounced deformities, all obviously of approximately the same degree of severity. Seedorff describes a woman, clearly a severe invalid chair case, who gave birth to a child with the lethal form of the disease.

It may be said, in summary, that whether a patient has the disease in a more severe or a mild form, it seems to be the rule — with few exceptions — that the children, when they inherit the gene, contract the disease in a degree of severity which is in close accord with that of the parents. The degree of severity, therefore, shows in general only small variations in any one family, but can vary greatly from family to family.

These facts should offer some guidance in the question of sterilization and abortion in the individual case.

In the milder cases it is probably justifiable to advise against abortion, giving the reason that if the expected child should show any symptoms of the disease, these would be of a relatively mild type. In the few cases where the question arises concerning persons with the disease in one of its most severe forms, there is reason, on the other hand, to advise

directly against child bearing, and even to advise sterilization.

It should always be taken into consideration, firstly that the risk of contracting the disease need never be estimated as being more than 1 : 2, and secondly that these patients are as a rule intellectually well equipped, and that their children do not run any greater risk of mental defects than normal individuals.

For these reasons, in reply to the questions from the three cases concerning abortion indications for eugenic reasons, the authors chose to advise against the idea, since they belonged to families who exhibited the disease in a relatively mild form.

As pointed out in the clinical analysis of the material, signs of an exacerbation of the osteoporotic condition in the disease have been observed in association with pregnancy and lactation in some cases. In one such case, vertebral compressions were developed which disabled the woman for more than a year, and also permanently worsened her mobility. In this special case, a further pregnancy was considered to hold so great a risk for the woman's own health, that sterilization was advised.

H. Social adaptability in regard to life at work and other living conditions

1. Ability of patients to support themselves

As may be seen in the previous account of the material, there are very varying degrees of physical handicap among these cases of osteogenesis imperfecta. It is obvious that the ability to support themselves will vary greatly among these individuals. It was evident from the discussion on school attendance, that certain of the patients had such a severe functional reduction that they were completely dependent upon the help of other people already at school age.

The ability for self-support does not however remain static. Some of those who were relatively slightly handicapped during childhood, encounter great difficulties which make it impossible from them to support themselves; others with severe handicap may be fortunate enough to find a suitable occupation. It is problems such as these, which will now be discussed.

For the sake of lucidity, the material will be classified here according to ability for self-support. No essential differences between the sexes were found in this respect, and the sexes will therefore be discussed in combination.

a) *Patients completely or partly incapable of supporting themselves.* Table 54 shows the number of cases in the material receiving an invalid pension at the time of the investigation. At the first glance at such a table, it may seem that the degree of inability for work and self-support closely follows the degree of movement handicap.

TABLE 54. *Number of cases of osteogenesis imperfecta over 16 years of age with invalid pension in different groups of physical handicap.*

Degree of handicap		Total No. of cases over 16 years	No. of these with invalidity pension because of			Invalidity pension previously because of osteog. imp. but not 1957
			osteog. imperf.	osteog. imp. + another disease	another disease only	
Men:						
None or slight		59	—	2	1	1
Fairly severe or severe		15	11	—	—	2
All men	No.	74	11	2	1	3
	%	—	14.9	2.7	1.4	4.1
Women:						
None or slight		52	3	1	2	—
Fairly severe or severe		10	8	—	—	—
All women	No.	62	11	1	2	—
	%	—	17.7	1.6	3.2	—
Both sexes:						
None or slight		111	3	3	3	1
Fairly severe or severe		25	19	—	—	2
All cases	No.	136	22	3	3	3
	%	—	16.2	2.2	2.2	2.2

The frequency of inability for work increases with increasing physical handicap, but the fact that there is no complete parallelism becomes evident in a closer study of the material. It is true that a physical handicap is a perpetual drag on the patient, but other factors play a great part, as is shown, not least clearly, by these particular individuals. The choice of work is, of course, of great importance as regards ability for self-support.

Patients completely unable to work. Of the 22 patients with osteogenesis imperfecta who were pensioned because of this disease alone, half consisted of individuals who were quite unable to contribute towards their support.

These latter can be divided into different categories:

1. Some of them, at the time of the investigation in upper middle age, had previously, because of a relatively successful choice of work, been fully or partially able to support themselves, and had been fairly well adapted. The progress of the disease, however, caused them to "age" rather early, with a reduction in efficiency.

2. For others, some attempt had been made towards occupational training, but the occupation did not help the patient to any great extent, as regards self-support. This group, for example, includes two seamstresses, who by their work only managed to earn a few hundred crowns per year.

3. In another two cases, occupations which had no attraction for them were suggested at the boarding schools for the handicapped, which they attended. The only suggestion made to one of them was training as a shoemaker, and since he was not interested in this work, he returned home with the feeling that there was nothing to be gained by an occupational training. He had later devoted much of his time at home to certain handiwork, and had also, amongst other things, studied languages by correspondence. He was to be denoted as quite unadapted as far as supporting himself was concerned, but in other respects he managed very well and was fairly content with his life. The other case had expressed a desire during his stay at boarding school to become a goldsmith. This could not be arranged, however, and it was suggested instead that he learned to knit. He returned home disappointed, and occupied himself with various things, such as radio repairs, language studies and anything that interested him, but his set-back had made him bitter, and a certain paranoid attitude developed.

4. The final category includes two examples, where neither the patients themselves nor the people in their surroundings considered it worthwhile to attempt any occupational training on account of their severe disablement. However, although quite incapable of contributing towards their support, they accepted their situation surprisingly well. They occupied themselves with reading and music, or handiwork, and were reasonably content with their lives.

Pensioned patients with some working ability. Two examples have been given above of cases of osteogenesis imperfecta who were considered so severely handicapped that not even an attempt was made at occupational training. Other cases were nevertheless found in the material who were just as badly handicapped, but who in spite of this were able, with their own determination and the help of others, to become either partially or fully able to work and support themselves. This is a fine illustration of how the degree of physical handicap need not play the major role in regard to the ability of the patients to work and support themselves.

As mentioned above, approximately half of the invalid-pensioned were able to carry out certain work and earn some income.

As in the case for those completely unable to work, different categories can be distinguished here:

One group consists of those who had 'aged' early through the progress of the disease, their working ability being seriously reduced.

In another category occupational training had worked out more satisfactorily, so that the patients, by means of their work, were able to reach a somewhat higher income, and could count on a constant annual income of about 2,000 crowns and in some cases 5,000 crowns. As a rule they appeared to be anxious to look after themselves to the greatest possible extent, even economically. In some cases at least, in spite of this generally positive attitude, the realistic problem was encountered of whether it would be wise to attempt to exceed the income limit, above which the invalid pension would be withdrawn; this particularly in consideration of the practical difficulties and the time involved if it should become necessary to apply for the pension again.

A third group, with the same "drive" and to some extent an even greater degree of optimism, consisted of young people who were working their way forward to better positions and a safer livelihood by means of different types of training. Two of them attended a trade school, one studied at a technical college, and one studied at university.

b) *Patients fully able to support themselves.* Two of the severely handicapped, also, did not receive a pension but supported themselves by their own work (see Table 54). The group of self-supporting individuals thus includes osteogenesis imperfecta patients of all grades of physical handicap, even those requiring invalid chairs.

The following seems relevant in this connection. The degree of physical handicap has been primarily used in this report to indicate the degree of impediment of movement. As so often happens in classifying, we have encountered

cases who were difficult to place. We have felt compelled to designate some cases as only slightly handicapped, on consideration of their mobility and ability to compensate for their anatomical defects. At the same time we have been conscious that the same defects in a patient with a less robust mental constitution would have justified an assessment as a greater degree of handicap. Regarding even those who were without any direct impediment to movement, there were many who had a certain handicap in other respects. The majority had to exercise great caution in order to avoid fractures, and many had a slender and weak body build, which is prejudicial in many respects. There were thus several patients in the less handicapped group with a functional reduction, which should undoubtedly have justified their receiving a pension. But because of a successful adaptation to their occupations, they were capable of completely supporting themselves.

2. *Requirements for the adaptability of the handicapped to working life*

a) *Early advice regarding occupation and early training (habilitation).* As indicated above, the choice of occupation played a very great part where the ability of the patients to support themselves was concerned. Only a few osteogenesis imperfecta patients, however, entered by the direct help of the community, in the form of occupational guidance, trade schools, or rehabilitation organizations, into the occupation where at the time of the investigation they were doing good work. Two women may be mentioned as examples. In spite of being dependent on leather supports and sticks in order to walk, they had never received an invalid pension. After being educated at boarding schools for the handicapped followed by vocational training, each of them obtained work which gave them satisfaction and made it possible for them to support themselves; one became a seamstress, and the other a telephonist. A third person (a man) passed the lower certificate examination at a boarding school for the handicapped, and at the time of the investigation was continuing studies at a higher commercial school. Training for more intellectual occupations, to a greater extent than has been carried out in previous years, would possibly be advantageous to these patients.

During the last few decades, the community has had increasingly great resources for the habilitation of handicapped people. Practically all osteogenesis imperfecta patients, even those with severe functional reduction, could probably become more or less completely adapted as

regards self-support, if all resources for vocational guidance and training were utilized in good time.

b) *Rehabilitation.* If rehabilitating treatment is regarded in a wide sense, and apart from ability tests, retraining and training for employment, such measures as orthopedic treatment with technical aids, and physio-therapy with movement exercises are included, it can be said that 45 (31 %) of the 144 patients over 16 years of age had received such treatment. For 24 (17 %) of these 45 patients the results could be regarded as positive. Only one had undergone ability tests, and two retraining, but 16 (11 %) had received training for employment. Twelve of them (8 %) considered that they needed more rehabilitating treatment, and 18 cases (12 %) were in need of such measures in the future, according to our assessment.

Early vocational guidance and training have not been included here under the heading of rehabilitatory treatment; this constitutes a direct continuation of school education.

Rehabilitation for these patients has not thus played the part that might have been desired. There is reason to suppose that, in the future, with an increased interest in rehabilitation activities, it will be possible to offer them increased assistance.

c) *Own choice of occupation.* For this group of handicapped people, their own choice of occupation seems to have been of more significance than either early vocational training or rehabilitation. This applies both to the group with and that without more or less severe impediment to movement.

The majority were successful in finding, on their own, an occupation in which they were effective and could earn their living. Several cases, who first sought help from the community for occupational training, with a poor result, appeared to have been more successful after taking the matter into their own hands and discovering for themselves an occupation which suited them. This was possibly simplified by the long period of full employment which had been achieved in the labour market.

Table 55 shows the distribution, into different industries, of economically active men and women in our series of cases, and, for comparison, the figures for the total population.

TABLE 55. *Economically active men and women with osteogenesis imperfecta distributed according to branch of industry, compared to the corresponding distribution in the general population 1950.*

Branch of industry	Men			Women		
	Osteog. imperf.		General population	Osteog. imperf.		General population
	No.	%	%	No.	%	%
A. Agriculture and ancillary trades	3	5	25.3	1	3	6.5
B. Building-trades	3	5	46.2	—	—	25.9
C. Manufacturing and handicraft trade	26	44		5	15	
D. Transport and communication	5	9	9.1	1	3	5.2
E. Commerce	15	26	11.7	16	49	28.0
F. General administration	2	3	7.0	4	12	22.6
G Professions	2	3		—	—	
H. Domestic service	—	—	—	5	15	11.0
I. Others	3	5	0.7	1	3	0.8
Total	59	100	100	33	100	100

There is a certain degree of underrepresentation in the agricultural and ancillary industries, and an overrepresentation in those industries which are officially described as "commercial". This applies to both sexes, and such a grouping is rather to be expected. The heavier occupations are avoided, while on the other hand the relatively light work, found in commerce and similar occupations, is more suitable for these patients with physical handicap.

The distribution of the material according to occupational positions as employers, salaried employees and wage-earners is shown in Table 56.

Employers are just as well represented among the individuals in this series with osteogenesis imperfecta as in the total population. The fact that so many with this disease were able to maintain themselves in this way may, of course, have been due to an endeavour to obtain such an independent position that they could arrange their work with regard to the special functional impediments from which they suffered. The fact that on an average they appeared to be well equipped intellectually, and

TABLE 56. *Occupational status of men and women with osteogenesis imperfecta compared with the corresponding figures for the general population in Sweden 1950.*

Sex	Total No. of economically active persons	thereof					
		Employers		Salaried employees		Wage-earners	
		No.	%	No.	%	No.	%
Osteogenesis imperfecta:							
Men	59	15	25.4	14	23.7	30	50.8
Women	33	4	12.1	11	33.3	18	54.5
Both sexes	92	19	20.6	25	27.2	48	52.2
General population:	-	%		%		%	
Men		22.5		20.4		57.1	
Women		10.4		46.0		43.1	
Both sexes		19.3		27.2		53.5	

that they often received a relatively good education, was also perhaps of some significance in this respect. The "drive" which we believe is a characteristic feature in these individuals, was certainly also of great help to them.

In the official classifications of industries and occupations, which have been used here, it is only possible to obtain a rough idea of whether or not the occupations represented there are suitable for a person with a particular physical handicap. Occupations of different grades of suitability may be found in every branch of industry, and to a certain extent also within each of the three occupational positions (employer, salaried employee, wage-earner).

Since it is primarily the demand of the occupation on physical strain and mobility that is the deciding factor for persons suffering from osteogenesis imperfecta, in choosing their work, we have attempted to classify the occupations occurring in this material from this viewpoint. For this purpose the type of trade or occupation has been regarded as of secondary importance, and social and occupational positions have been disregarded. Each case has been assessed individually.

The classification has given the following 9 groups:

Group 1: Active and heavy work of type: farm worker, unskilled labourer.

Group 2: Active work of type: skilled worker, carpenter, plumber, turner, fitter.

Group 3: Industrial work of type: factory worker, textile and metal worker.

Group 4: Active work of type: workmen's foreman, manager, chief storekeeper, restaurant-keeper.

Group 5: Active work of type: shopkeeper, male nurse, caretaker, fireman, shop assistant, waitress, bakeress, store worker.

Group 6: Domestic work of type: housewife, housekeeper, domestic servant, charwoman, under-cook.

Group 7: Sedentary work of type: office- and other lighter clerical work, teacher, pastor, telephonist, clerk, draughtswoman, tobacconist, student.

Group 8: Other sedentary work of type: watchmaker, engraver, instrument maker, seamstress, tailor, shoemaker, ice cream salesman, motor winder, typographer.

Group 9: Pensioner (old-age and invalidity).

The demand on physical strain in the groups lessens with increasing group numbers. The same holds for the demand on mobility from group 7 onwards.

Following this principle, Table 57 shows the economically active patients of both sexes, and also housewives and students over 16 years of age. Group 9, comprising those receiving old-age and invalid pensions (14 % of those over 16 years of age), is not included.

The table shows accumulations of non-handicapped men in both group 5 (light, active type of occupation) and in group 7 (sedentary work of the clerical type). Non-handicapped women are found mainly in group 6 (domestic work), and also in group 7. Men with slight, and also with severe impediment to movement, are found as expected in the sedentary occupations. The same also applies to a certain extent to the women, the majority of whom however, without or with slight handicap, are found in group 6 (domestic work). In this group also, the patients have some opportunity of adapting their work according to their handicap.

These patients with osteogenesis imperfecta, often handicapped in one

TABLE 57. *Men and women over 16 years of age with osteogenesis imperfecta distributed firstly according to the bodily strain and mobility demanded by their occupation, secondly according to the type of occupation.*

Sex	Group	Degree of handicap						Total	
		None		Slight		Fairly severe and severe			
		No.	%	No.	%	No.	%	No.	%
Men	1—2	11	28.2	2	14.3	*1	11.1	14	22.6
	3—4	8	20.5	—	—	—	—	8	12.9
	5—6	13	33.3	1	7.1	—	—	14	22.6
	7—8	7	17.9	11	78.6	8	88.9	26	41.9
	Total	39	100	14	100	9	100	62	100
Women	1—2	—	—	—	—	—	—	—	—
	3—4	—	—	—	—	—	—	—	—
	5—6	27	69.2	10	90.9	—	—	37	67.3
	7—8	12	30.8	1	9.1	5	100.0	18	32.7
	Total	39	100	11	100	5	100	55	100

* carpenter with his own workshop.

respect or another, have to a great extent found suitable work. But the way there has, for many, meant repeated trials and bitter failures. They have often found, after attempting an occupation over a longer or shorter period, that they could not hold the position and that it was necessary to try to find other more suitable work.

In planning this investigation, it was hoped to obtain information of a practical nature as regards this particular problem of how the severely disabled manage to find suitable work, and what work was found most suitable.

Table 58 shows the number of men and women over the age of 16 years, who had changed their occupation because of their handicap, and the way in which they managed to remain selfsupporting.

In Table 59 those occupations are shown which the patients in Table 58 had attempted up to the time of the investigation.

TABLE 58. *The occurrence of men and women with osteogenesis imperfecta over 16 years of age, who by changing occupation retained different degrees of ability for self-support.*

Handicap	Total No. of patients over 16 years of age	No. of those who changed occupation, resulting in ability to support themselves					
		full ability		partial ability		inability	
		No.	%	No.	%	No.	%
Men:							
No handicap	42	4	9.5	—	—	—	—
With handicap	32	5	15.6	2	6.3	—	—
All men	74	9	12.2	2	2.7	—	—
Women:							
No handicap	41	2	4.9	—	—	—	—
With handicap	21	—	—	1	4.8	1	4.8
All women	62	2	3.2	1	1.6	1	1.6
Both sexes:							
No handicap	83	6	7.2	—	—	—	—
With handicap	53	5	9.4	3	5.7	1	1.9
Total	136	11	8.1	3	2.2	1	0.7

Of especial interest is the progress made by some of the most severely handicapped patients. A 26 year old man had at the age of 14 years applied by himself for a place in the engraving industry, in which he progressed with the help of evening courses. He liked his work and had an annual income of 12,000 crowns. — A 30 year old man who had spent altogether about 6 years in hospital for his fractures, and who at the time of the investigation was able to walk with the help of a leg support and an elbow rest, had at the age of 16 years tried working as a goldsmith for six months, but had to give this up because of his left handedness. He then began work as an instrument maker, and in this he progressed very well. At the time of the investigation he had an annual income of 12.000 crowns. — A 36 year old man, whose physical handicap was one of the most severe of all the cases examined, but who was more fortunate as regards his economic prospects and intellectual status, had under the guidance of a private teacher studied for a university degree, and was continuing with university studies. He had a rising income as a literary critic. — A 27 year old man, who because of deformities had been unable to walk since the age of 8 years, and could only go on all fours, had wanted to train as a fine mechanic at a trade school for the handicapped. As there was no place for him in this type of work, he returned home and began selling hot sausages and ice cream.

ABLE 59. *Occupations tried by certain patients with osteogenesis imperfecta and the result thereof in ability to support themselves.*

Age at exam.	Reason for change of occupation	Degree of physical handicap	No. of fract.	Types of occupation tried by patients	Ability of self-support full	partial	none
44	Deafness	Slight	1	Charwoman + nightnursing — occasional cleaning		+	
60	Fractures + deformities	Fairly severe	7	Domestic work — shopassistant — office worker — light household work			+
53	Fractures + deformities	Slight	11	Advertising agent — tobacconist	+		
26	Bone fragility	None	9	Messroom attendant — office worker — chauffeur — storekeeper	+		
19	Fractures	Slight	45	Turner — fitter — storekeeper — typographer apprentice	+		
40	Fractures + knee-injury	None	7	Factory worker — stoker on a canalboat — electric welder — storekeeper	+		
31	Deformity + lower back trouble	None	4	Farm worker — fine mechanic and forging apprentice — — vehicle body worker	+		
51	Bone fragility	Slight	20	Farm worker — country shopkeeper — cashier	+		
56	Lower back trouble	Slight	10	Forestry worker — factory worker — watchman	+		
41	Deafness	None	4	Waitress — charwoman	+		
38	Fract. + low back trouble	Slight	25	Laborer — assistant truckloader — trammer, greaser, stoker — laborer — kiosk manager		+	
22	Fractures + deformities	Slight	5	Messroom attendant — factory worker — office worker	+		
31	Low back trouble	None	1	Domestic worker — cafe waitress — office worker (+ housewife)	+		
54	Deafness	None	2	Shoe factory worker — chauffeur to brewery — storekeeper	+		
39	Fractures + deformities	Fairly severe	35	Draughtsman (difficulty in getting to work) — carpenter (own workshop)		+	

He also worked with motors. He had supported himself since the age of 17 years, had bought his own car and together with his father a two-family house, in which he occupied the upper apartment. He had an annual income of about 12.000 crowns. — A 28 year old man had between 3 and 7 years of age spent the greater part of his time at a cottage hospital in his home district due to fractures, and had subsequently stayed at a boarding school for the handicapped until he was 13 years old. He was completely confined to an invalid chair because of deformities. After returning home he worked for about two years at machine knitting, and then at assembly work for an employment training institute. At the age of 24 years he set up a typewriting bureau, bought duplicating machines, and started his own advertisement paper for the district. Four years after beginning the business he had as much work as he and an assistant had time for. The gross annual turnover was approximately 60.000 crowns, and he planned to extend the business further.

3. Income

The income earned by a person may be considered as some measure of his social adaptation. It is therefore of interest to study the annual income of patients with osteogenesis imperfecta.

Table 60 shows the distribution of different incomes, both for men and for married and single women with different degrees of handicap.

The mean income for men and single women (economically active) with different grades of handicap is shown in Table 61.

Economically active individuals in this series are apparently on approximately the same level as the general population, as regards income. The mean income is in fact somewhat higher than that given for the total population in 1956. The mean income for employed men in the total population in 1956 was approximately 9.600 crowns, and for single, employed women approximately 5,000 crowns.

4. Housing standard

The standard of housing was recorded for these patients, both in order to obtain some idea of the extent to which it appeared to fulfil the minimal requirements of the patient, and also as a further measure of the social adaptation in this series of cases.

Table 62 gives some information from which an assessment of the

TABLE 60. *Annual income of patients over 16 years of age (15 cases not included because of lacking information.)*

Annual income, Swedish Cr.	No or slight handicap		Fairly severe or severe handicap		All cases	
	No.	%	No.	%	No.	%
Men:						
No income	5	9.6	1	7.7	6	9.2
Invalid pension only	7	13.5	6	46.2	13	20.0
Income (excl. pension):						
under 4,000	—	—	1	7.7	1	1.5
4—8,000	4	7.7	1	7.7	5	7.7
8—10,000	12	23.1	—	—	12	18.5
10—15,000	19	36.5	4	30.8	23	35.4
over 15,000	5	9.6	—	—	5	7.7
Total men	52	100	13	100	65	100
Women:						
No income	20	43.5	—	—	20	35.7
Invalid pension only	6	13.0	5	50.0	11	19.6
Income (excl. pension):						
under 4,000	4	8.7	3	30.0	7	12.5
4—8,000	9	19.6	2	20.0	11	19.6
8—10,000	2	4.3	—	—	2	3.6
10—15,000	4	8.7	—	—	4	7.1
over 15,000	1	2.2	—	—	1	1.8
Total women	46	100	10	100	56	100

TABLE 61. *Average annual incomes (Sw. Kr.) of economically active men and single women with osteogenesis imperfecta in different handicap groups.*

Degree of handicap	Men		Women		Both sexes	
	No.	Average income	No.	Average income	No.	Average income
None	31	12,974	11	6,373	42	11,245
Slight	9	9,722	1	(3,000)	10	9,050
Fairly severe and severe	6	8,500	4	2,600	10	6,140
Total	46	11,754	16	5,219	62	10,068

TABLE 62. *Housing standards for patients with osteogenesis imperfecta with different degrees of physical handicap.*

Housing standards	No handicap (119)		Slight handicap (32)		Fairly severe and severe handicap (35)		All with handicap (67)		Total (186)	
	No.	%	No.	%	No.	%	No.	%	No.	%
With own house	50	42.0	14	43.8	15	42.9	29	43.3	79	42
Rented apartment	69	58.0	18	56.3	20	57.1	38	56.7	107	57
No central heating, nor w. c.	18	15.1	11	34.4	5	14.3	16	23.9	34	18
With c. h. and/or w. c.	22	18.5	5	15.6	7	20.0	12	17.9	34	18
With c. h. + w. c. + bath room	79	66.4	16	50.0	23	65.7	39	58.2	118	63
$>$ 1½ person per room	36	30.3	10	31.3	4	11.4	14	20.9	50	26
$\leq$ 1½ person per room	83	69.7	22	68.8	31	88.6	53	79.1	136	73

standard of housing can be made. Of 186 apartments, 11 (6 %) were so old and old-fashioned that they had to be denoted as sub-standard, the rest were moderately good or good. One fairly severely handicapped woman lived in a new and modern apartment, but this was denoted as not sufficiently suitable, as it was 1½ flights from ground level with no lift, and the patient could not get in and out without help. In the case of 24 other handicapped patients, some small desires were expressed, which, could they have been realised, would have made the patients more comfortable. Otherwise in general the living accommodations were well suited for the patients' conditions. Special arrangements had been made in the apartments of two patients with severe impediment to movement, who used invalid chairs, so that they were more independent.

In order to assess whether or not there was any overcrowding, the norm which Roos (1949) named as the ideal minimal housing standard was used; this meant that a maximum of 1½ person units were allowed to occupy one room unit, children being counted as one person unit, and any room under 6 m², and similarly the kitchen, not being counted

as a room unit. The housing conditions of just over 70 % of the osteogenesis imperfecta patients attained this norm.

Of the 186 apartments concerned, in 101 cases it was the patients themselves with husband or wife who were responsible for the apartment, and in 85 cases the parents or other close relatives of the patients. The housing standard was possibly somewhat higher for those patients whose parents or other relatives were responsible for the apartment. However, there was no essential difference.

On the whole, the housing standard for this group of the community must be denoted as satisfactory.

J. Discussion and conclusions

This series of cases of osteogenesis imperfecta has been studied from several different aspects. Throughout the investigation interest has been concentrated on the question of how those suffering from this disease have adapted themselves in different respects to the community.

In a number of cases the disease led only to increased morbidity, with longer or shorter periods in hospital, or absences from school or work. Those patients with intact mobility functions are not of course of such great interest as those with more impairment of movement, as regards the study of the effect of the disease on social adaptation.

Even patients with very serious functional reduction often had an amazing ability for adaptation.

In attempting to explain this observation, it may be wondered whether these individuals have any special intellectual or other qualities. A remarkable number managed to continue their education beyond the primary level. At least as great a proportion as that in the general population worked their way forward to positions as employers. During the interview and examination an attempt was made to assess the intellectual capacity of every patient, and an assessment recorded. This assessment was complemented to the greatest possible extent by information from relatives and other people. Allowing for the sources of error which may occur in making such an assessment without objective intelligence tests, on an average a strikingly high intellectual capacity was found in these individuals.

Not least in those with pronounced impediment of movement, a

positive attitude, optimism and "drive" were encountered throughout in these patients. This opinion was also expressed in several cases by relatives and hospital personnel. These severe cases were often said by their families to be of a very even temperament.

This good mental balance and optimism was of such frequent occurrence, that it can hardly be doubted that it is a real phenomenon in these patients. It is difficult, however, to produce any sound explanation. There is conceivably some connection with the early onset of the disease, and the fact that the patients have had to learn to live with difficulties since early childhood. Another possible factor is the special understanding which they may have received from their families and friends. It would be interesting to know whether the same observation can be made in other groups of people who have been afflicted from childhood by a severe physical disability.

The optimism and "drive" observed in these individuals with osteogenesis imperfecta has been expressed in various ways. Many of them obtained a vocational training and worked their way forward to positions as salaried employees or employers. It was pointed out in the account of the distribution of this material into towns, other built up areas and sparsely populated areas, that a relatively greater number of these patients than the general population lived in towns and other built-up areas. This may indicate that these persons chose the more built-up areas in order to have better opportunities of earning a living in spite of their handicap.

The case reports have revealed almost unbelievable achievements of very severely disabled patients.

When their work proved altogether too difficult, they seldom gave up, but attempted to find another occupation which they were able to master.

There are in fact many lessons to be learned from a study of such a disease as osteogenesis imperfecta.

With few exceptions, the patients appeared to have learned to accept their disease with the difficulties which it often involves, and were able to adapt themselves well to life and to the community. They had managed to a great extent to co-ordinate their physical, mental and social abilities, so that in many cases they could be regarded, from the socio-medical aspect, as fully adapted. As Ruesch so aptly points out,

one would be almost inclined to regard them as healthy in spite of their disablement (cf. page 176).

As practical conclusions which may be drawn from this study, we would like to mention a few special points.

In assessing the possibilities of a person of making his way in life, one should not be guided too closely by the observations made in a general physical examination. The attitude of the patient to the surrounding world and to his own situation and handicap and his intellectual capacity is of much more importance.

Vocational training and rehabilitation may be greatly desirable, even when the physical function appears to be extremely deficient. Whether such training proves to be successful depends to a great extent on the intellectual capacity and the will of the patient. The interest and inclination of the patient should thus be considered to the greatest possible extent.

It is only to be expected, that a number of the most severely affected cases, in spite of their attempt to support themselves, have found it necessary to make use of the financial assistance offered by the community in the form of a pension. If, even so, they carry out some form of work, and are successful in reaching a certain income level, there is a threat of pension withdrawal. It is natural that they then feel rather insecure, and hesitate before making the step that would mean giving up their pension. It is true of practically all who receive a pension because of osteogenesis imperfecta, that at any time they may sustain a fracture or some other complication as a result of their bone fragility and osteoporosis. This may result in inability to work for an indefinite period. In consideration of this, and also of the extra expenses which are constantly incurred for medical care, technical aids, transport etc., it seems well worth considering whether these patients — and also similar cases in other disease groups — should not be allowed to retain their pension as a protection, even if for a shorter or longer period they manage to reach a normal income. With the "drive" and other positive traits which are often encountered in these patients, this would probably constitute a spur to continued useful work.

Osteogenesis imperfecta is a particularly interesting disease from the clinical and genetic aspect. Not, however, until the socio-medical side of the disease is also studied together with these two aspects, can a more complete picture of its manifestations be obtained.

At the first sight of such patients in a hospital ward, one tends to regard them as severely affected, anatomically and functionally. The impression is easily obtained that they represent a group of afflicted people who most likely constitute a burden to the community both economically and from the point of view of medical care. We hope that by this study we have been able to give a clearer picture of the true place of this group in the community.

K. Summary socio-medical aspects

Probably because of its rareness osteogenesis imperfecta has seldom been subjected to any systematic investigations. There is no known systematic socio-medical investigation of this disease. As part of an investigation of a material of osteogenesis imperfecta in Sweden, a report is made here of a socio-medical study of 190 individuals with osteogenesis imperfecta, who were personally interviewed and examined. A preliminary account of the early stages of the investigation was published in 1956.

A very brief account of some essential characteristics of the disease and of the material and methods used in this investigation is given first. These matters are, however, treated in greater detail in the foregoing section, dealing with the clinical and genetic aspects. It is estimated that the material includes approximately 60 per cent of the persons with osteogenesis imperfecta in Sweden.

Sixty per cent might seem somewhat too small a number to use as a basis for a socio-medical assessment of the disease. The defects of the material are discussed. There are grounds to believe that the material, in spite of its defects, may be regarded as well suited for a socio-medical study of the disease.

Some considerations of disabling diseases in general are discussed in a study of the literature, in particular the rheumatic diseases, which are often associated with impediment of movement. Reference is made to their great social and economic significance, and the concept of "partial working ability" is clarified from a statement made by the Committee for the Partially Disabled (1946). Finally, some aspects are discussed of those factors which, apart from the purely physical handicap, may be of importance in social adaptation.

This series of cases has been considered as particularly suitable for a socio-medical study of these questions, being well demarcated and easily surveyed, and at the same time including all grades of physical handicap.

In a survey of the distribution of the material in different respects, the following points are mentioned. Proportionately the incidence is somewhat greater in towns and other built-up areas. The geographical occurrence, is, however, on the whole in agreement with the map of the general population. As regards physical handicap, it is found that only 19 % of the total have more pronounced impediment of movement, 17 % have slight impediment of movement and 64 % are without such impediment. It is pointed out, however, that the majority suffer some difficulties on account of their disease.

In a section concerning the burden placed by the disease on the local health services, some figures are given regarding the total and mean number of fractures, medical attendances, medical transport with distances covered, and total and average periods in hospital.

It is evident that this small section of the population occupies an unproportionately large number of the hospital beds.

The general school education has been satisfactory. When attendance at an ordinary primary school was not possible, the patients were either educated at boarding schools for the handicapped or at home; this was or had been necessary in 21 % of all patients between the ages of 8 and 39 years, namely 19 individuals with severe impediment of movement and two with slight impediment to movement. It is of interest that there seems to have been a greater attendance at schools above the primary stage among these patients than in the total population.

As regards family formation, the marriage frequency for the non-handicapped is almost as high as for the total population, but decreases, as expected, with increasing disablement. It is difficult to compare the mean number of children per marriage in these persons with that of the total population, since there are no directly comparable figures for recent years. It could be established with some degree of certainty, however, that the mean number of children and the fertility in the less handicapped were only slightly lower than the figures for the total population during a corresponding period.

In a discussion concerning the indications for abortion and sterilization in osteogenesis imperfecta the following was pointed out. The disease is to be denoted as genetically dominant. The risk therefore that an ex-

pected child contracts the disease is 50 %, when one of the parents has the disease. There seems to be reason to believe that the degree of severity of the disease, if inherited, deviates only exceptionally from that of the parents. The indications should therefore be weighed in consideration of the degree of severity in every individual case.

The ability of the patients to support themselves has been discussed. It is found that even a relatively large number of the severely handicapped are surprisingly well adapted in this respect. The occurrence of early vocational training and rehabilitation with the help of the community, and the patients' own choice of occupation are described, and their importance is discussed. The income level for the economically active patients in this material is found on the whole to be fully comparable with that of the average population. A survey of the housing conditions of the patients shows a good standard.

It is pointed out in the final discussion, how patients even with a very severe functional reduction often show a surprising ability to adapt themselves to the community. Various possible factors which may be of importance for adaption are discussed. The general mental state of the patient, his psychological balance and attitude to his own situation, and not least his intellectual capacity, seem to be more important factors in this respect than the reduction in physical function.

Survey of clinical data (Tables 63 and 64)

A survey of the clinical data of the 274 cases of osteogenesis imperfecta comprising the total material is presented in Tables 63 and 64.

Table 63. Surviving cases = Osteogenesis imperfecta tarda.

1. Identification number: The material has been classified into units, each comprising a sibship and its parents. Each sibship has been given a number, with the number of its members in order of birth. Thus No. 8:5 indicates the fifth child in sibship No. 8. The father of sibship No. 8 is recorded as 8: F and the mother as 8: M. When the father or the mother in turn belongs to a sibship with osteogenesis imperfecta, this is indicated as 7: 2 = 8: F or 8: F (= 7: 2). Within any one pedigree, earlier generations are given lower numbers than later generations. Probands are indicated by 'p', e. g. 10: Mp.

The sibships have, further, been placed into four different groups according to the occurrence of the disease in the family, thus:

Group 1, sibships 1—87: Pedigrees with two or more cases in two or more generations.

Group 2, sibships 94—98: Pedigrees with two or more cases in only one generation. In two of these families the disease was lethal (so called congenital cases), and in three of the families the disease was compatible with life (so called tardive cases).

Group 3, sibships 100—117: Pedigrees with isolated lethal 'congenital' cases.

Group 4, sibships 120—174: Pedigrees with isolated surviving 'tardive' cases.

2. Mode of information: Ex = examined by author. H = hospital record. R = reliably reported from non professional observers, usually relatives.

3. Sex: m = male. f. = female.

4. Age at examination or death (†) is given in years.

5. Marital status: s = single. m = married. d = divorced. w = widowed.

6. Total number of children in this sibship: includes both affected and non-affected.

7. Sporadic cases are indicated by +.

8. Degree of physical handicap: 0 = none; sl = slight; f = fairly severe; s = severe.

9. Number of fractures: + = fractures reported but number not known.

10. Age at first fracture: y = years; m = months; d = days.

11. Deformities of extremities: sl = slight; m = moderate; s = severe.

12. Deformity of spine: sl = slight; m = moderate; s = severe.

13. Low back trouble and other spinal symptoms are indicated by +.

14. Abnormal shape of skull is indicated by +.

15. Body height is given in centimetres (cm.).

16. Characteristic dental changes are indicated by +.

17. Hyperlaxibility and/or distortions: +.

18. Pes plano-valgus: +.

19. Blue sclerotics: +.

20. Arcus corneae: +.

21. Deafness: sl = slight; s = severe; v = very severe; + deafness reported but degree unknown.
22. Age at onset of deafness: years.
23. Comments: complementary remarks.

Lack of information is indicated by the sign*. Horizontal lines in Table 63 from above case No. 1: M to below case No. 97: 6 p indicate that those cases listed between two such lines belong to one and the same family.

Table 64. Lethal cases = Osteogenesis imperfecta congenita.

1—3. See table 63.
4. Age at death: y = years; m = months; d = days; i. u. = in utero; s. p. = sub partum.
5. Total number of children in this sibship: includes both affected and nonaffected.
6. Sporadic cases are indicated by +.
7. Number of fractures: + = fractures reported but number not known.
8. Deformities: sl = slight; m = moderate; s = severe.
9. Age at with fractures and/or deformities were observed: B = at birth; d = days.
10. Disturbed ossification of cranial bones.
11. Blue sclerotics.
12. Arcus corneae.
13. Observed arteriosclerotic changes of bloodvessels.

Lack of information is indicated by the sign *.

TABLE 63. *Survey of clinical data.*

Identification number	Information	Sex	Age at examination or death (†)	Marital status	Total number of children in this sibship	Sporadic case	Degree of physical handicap	Number of fractures	Age at first fracture	Deformities of extremities	Deformity of spine	Lower back trouble and other spinal symptoms	Abnormal shape of skull	Body height (cm)	Characteristic dental changes	Hyperlaxibility and/or distortions	Pes plano-valgus	Blue sclerotics	Arcus corneae	Deafness	Age at onset of deafness (years)	Comments
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Osteogenesis imperfecta in 2—6 generations:																						
1: M	Ex	f	67	m	7	+	sl	7	29y	sl	sl	+	–	139	?	+	+	+	+	v	36	
1: 1 = 2: F	Ex	m	44	m	1	–	0	12	10y	sl	–	+	–	169	–	+	–	+	–	–	–	
2: 1p	Ex	m	10	s	1	–	0	9	14m	sl	–	–	–	135	–	–	+	+	–	–	–	
3: F	R	m	63†	m	*	*	*	+	*	*	*	*	*	*	*	*	*	+	*	*	*	
3: 1?	R	f	86	s	4	–	*	>3	*	*	*	*	*	*	*	*	*	*	*	*	*	Living in USA
3: 2? = 4: M	R	f	80†	m	4	–	*	2	*	*	*	*	*	*	*	*	*	+	*	+	*	
4: 1	R	f	51	m	2	–	*	4	17y	*	*	*	*	*	*	*	*	+	*	*	*	Living in USA
4: 2 = 5: F	Ex	m	49	m	2	–	0	8	6y	sl	sl	–	+	165	–	–	+	+	+	sl	40	
5: 1p	Ex	f	17	s	1	–	0	10	3y	sl	–	+	–	145	–	+	+	+	–	–	–	

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
6: M	R	f	*†	m	*	*	*	*	*	*	*	*	*	*	*	*	*	+	*	*	*	
6: ? = 7: F	R	m	*†	m	*	—	*	*	*	*	*	*	*	*	*	*	*	+	*	*	*	
7: 2 = 8:F	R	m	74†	m	5	—	*	>5	*	*	*	*	*	*	*	*	*	+	*	+	50	
7: 5 = 9: Fp	H	m	70†	d	5	—	*	3	*	*	m	*	*	155	*	*	*	+	*	v	—	
8: 5	Ex	f	38	s	8	—	0	4	7y	—	—	+	—	159	—	+	—	+	+	sl	35	Exacerbation during pregnancy.
8: 7 = 10: Mp	Ex	f	34	m	8	—	sl	9	3y	—	sl	+	—	146	—	+	+	+	+	sl	28	
10: 1p	Ex	m	6	s	1	—	sl	5	10m	sl	—	—	—	*	—	+	+	+	—	—	—	
9: 1 = 11: M	Ex	f	44	m	1	—	sl	1	4y	—	—	+	—	*	—	—	—	+	+	v	10	
11: 1p	Ex	f	16	s	2	—	sl	3	11y	sl	sl	—	—	157	—	—	—	+	—	—	—	
11: 2p	Ex	f	14	s	2	—	0	5	2y	—	—	+	—	160	—	+	+	+	—	—	—	
12: F	R	m	61	m	*	*	*	+	*	*	*	*	*	*	*	*	*	+	*	v	45?	
12: 3p	Ex	f	27	s	3	—	0	3	2y	sl	—	—	—	*	—	+	+	+	—	—	—	
12: 2 = 13: F	Ex	m	28	m	3	—	0	4	10y	sl	—	—	—	172	—	+	—	+	—	—	—	
13: 1p	Ex	m	4	s	1	—	0	9	1y	sl	—	—	—	105	—	—	—	+	—	—	—	
14: M	R	f	60	m	*	*	*	+	*	*	*	*	*	*	*	*	*	+	*	*	*	
14: 1	R	f	62	m	9	—	*	+	*	*	*	+	*	*	*	*	*	+	*	*	*	
14: 2	R	f	79	m	9	—	*	*	*	*	*	*	*	*	*	*	*	+	*	*	*	Living in USA
14: 7	Ex	m	67	m	9	—	sl	6	14y	sl	—	+	—	150	—	—	—	+	+			History of otitis Slight deafness
14: 8p	H	f	57†	s	9	—	*	7	8y	*	*	+	*	*	*	*	*	+	*	*	*	
14: 9	Ex	m	60	s	9	—	f	9	12y	sl	sl	+	—	*	—	+	—	+	+			History of otitis Slight deafness

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
15: 1p	Ex	m	53	m	1	—	sl	11	1y	sl	m	+	—	141	—	+	—	+	+	—	—	
16A: 2	R	f	*†	m	*	—	*	+	*	*	*	*	*	*	*	*	*	*	*	*	*	
16A: 1? = 16: F	R	m	50†	m	*	—	*	+	*	*	*	*	*	*	*	*	*	*	*	+	*	
16: 2 = 17: F	Ex	m	78	m	4	—	*	8	*	sl	—	+	—	157	—	—	—	+	*	v	40	
16: 4	R	f	*†	*	4	—	*	+	*	*	*	*	*	*	*	*	*	*	*	+	*	
17: 1 — 18:Mp	Ex	f	51	m	2	—	0	7	1m	—	—	+	-	152	—	+	+	+	+	sl	<1	Improved hearing after fenestration op.
18: 2p	Ex	m	26	m	4	—	0	11	9m	—	—	—	—	165	—	+	+	+	—	v	21	Deafness of right ear.
18: 4p	Ex	m	19	s	4	—	sl	45	14m	m	—	+	—	163	—	+	+	+	—	sl	10	
20: M	H	f	60†	m	*	—	*	+	*	*	*	*	*	*	*	+	*	+	*	*	*	Of foreign birth.
20: 3p	H	m	32†	m	3	—	*	19	1y	*	*	*	*	*	*	+	*	+	*	*	*	Of foreign birth.
21: 1 = 22: M	R	f	48†	m	10	—	*	+	*	*	*	*	*	*	*	*	*	+	*	*	*	
21: 3	R	m	*†	*	10	—	*	+	*	*	*	*	*	*	*	*	*	*	*	*	*	
21: 5	R	f	74†	m	10	—	*	>3	*	*	*	*	*	*	*	*	*	+	*	*	*	
21: 6 = 23: M	R	f	80†	m	10	—	*	+	*	*	*	*	*	*	*	*	*	+	*	v	*	
21: 8	Ex	m	82	m	10	—	0	2	50y	sl	sl	+	—	150	—	+	+	+	+	s	35	
22: 1p	Ex	f	61	m	1	—	sl	3	11y	—	sl	+	—	136	?	+	—	+	+	—	—	
23: 2	Ex	f	66	m	9	—	0	11	2y	—	—	—	—	154	—	+	—	+	+	v	30	
23: 4p	Ex	m	61	m	9	—	sl	10	2y	sl	sl	—	—	158	—	+	—	+	+	v	15	
23: 7	Ex	m	57	m	9	—	0	3	13y	sl	—	+	—	176	—	+	—	+	+	sl	35	
24: F	Ex	m	40	d	5	+	0	7	2y	—	sl	+	—	176	—	+	+	+	+	sl	*	

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
24: 11p	Ex	f	11	s	1	—	0	10	1½y	sl	sl	+	—	143	—	+	+	+	—			History of otitis. Slight deafness.
25: F	Ex	m	60	m	*	*	0	1	35y	—	—	—	—	*	—	—	—	—	—	sl	<1	
25: 1	Ex	m	31	m	5	—	0	3	2y	—	sl	+	—	168	+	—	+	—	—	—	—	
25: 3p	Ex	m	25	s	5	—	0	9	8y	sl	sl	+	—	182	+	—	+	—	—			History of otitis. Slight deafness.
26: F	Ex	m	50	d	10	+	0	2	2y	—	sl	+	—	169	—	+	+	+	+	—	—	
26: 3p	Ex	m	9	s	3	—	0	6	2y	—	sl	—	—	*	—	+	—	+	—	—	—	
27: M	Ex	f	62	s	1	*	0	2	46y	—	sl	+	—	151	—	+	+	+	+	s	40	
27: 2=28: M	Ex	f	35	m	2	—	0	1	1½y	sl	—	+	—	154	—	—	—	+	—	—	—	
28: 1	Ex	f	16	s	4	—	0	1	1½y	—	sl	—	—	156	—	—	—	+	—	—	—	
28: 2p	Ex	m	14	s	4	—	0	3	13y	—	—	—	—	156	—	—	—	+	—	—	—	
28: 4p	Ex	f	7	s	4	—	0	0	—	—	—	—	—	113	—	—	—	+	—	—	—	
30: Fp	Ex	m	26	m	2	—	sl	55	1½y	sl	—	—	—	173	—	+	+	+	—	—	—	Of foreign birth.
30: 2p	Ex	m	2	s	2	—	0	0	—	—	—	—	—	*	—	+	—	+	—	—	—	Of foreign birth.
31: Fp	Ex	m	51	m	3	+	sl	12	3y	sl	sl	+	—	159	+	+	—	+	+	sl	51	
31: 1p	Ex	m	22	m	1	—	0	4	4y	—	—	+	—	159	—	+	—	+	—	—	—	
32A: F	R	m	*†	m	*	*	*	+	*	*	*	*	*	*	*	*	*	*	*	*	*	
32A: 3? = 32: Fp	H	m	72†	m	5	—	*	5	*	*	*	+	*	*	*	*	*	+	+	*	*	

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
32: 1p	Ex	f	48	m	3	—	sl		11	14y	sl	—	—	148	—	—	—	+	—	sl	44	
32: 3	Ex	m	42	m	3	—	0	4	6y	sl	—	—	—	158	—	+	+	+	+	—	—	
33: M	R	f	64†	m	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	
33: 5 = 34: M	Ex	f	42	m	7	—	0	0	—		—	—	—	163	—	+	—		—	—	—	
33: 6	R	f	18†	s	7	—	*	0		*	*	*	*	*	*	*	*	+	*	*	*	
33: 7	Ex	f	34	m	7	—	0	0			—	—	—	172	—		—	+	—	—	—	
34: 1p	Ex	m	14	s	2	—	0	12	1y		sl		—	156	—		+	+	—	—	—	
35: Fp	Ex	m	47	m	4	—	0	7	5y			—		171	—	—	+	—	—	—	—	
35: 2p	Ex	m	11	s	2	—	0	3	2y	sl	—	—	—	144	—		—	—	—	—	—	
36: F	Ex	m	56	w	7	+	sl	9	21y	sl	—		—	172	—	+	—	+	+	—	—	
36: 3	Ex	f	18	s	4	—	0	2	6y		—	—	—	163	—	+	—	+	—	—	—	
36: 4p	Ex	m	18	s	4	—	0	2	1y	—	sl	+	—	168	—	+	+	+	—	—	—	
37A: 2 = 37: M	Ex	f	55	m	5	+	sl	1	34y	—	m	+	—	142	—	—	—	+	+	s	9	Deafness of right ear.
37: 2p	Ex	f	20	s	5	—	f	16	3y	s	sl	+	+	*	—	+	—	+	—	—	—	
37: 4p	H	f	9†	s	5	—	*	2	2½y	*	*	*	*	*	*	*	*	+	*	*	*	
38: M	R	f	95†	m	*	*	*	*	*	*	*	*	*	*	*	*	*	+	*	*	*	
38: 5 = 39: F	Ex	m	65	m	6	—	0	6	3y	sl	sl	—	—	163	—	—	+	+	+	—	—	
39: 3 = 40:Mp	Ex	f	30	m	3	—	0	1	5y	—	—	+	—	147	—	+	+	+	—	—	—	
40: 1p	Ex	m	12	s	2	—	0	10	2y	—	—	+	—	130	—	+	—	+	—	—	—	
40: 2p	Ex	f	10	s	2	—	0	5	2y	sl	—	—	—	129	—	+	—	+	—	—	—	

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
42: M	R	f	44†	m	5	*	*	>4	*	*	*	*	*	*	*	*	*	+	*	v	*	
42: 1p	Ex	f	40	s	4	—	sl	2	13y	sl	—	+	—	152	—	+	—	+	—	sl	*	Deafness of left ear.
42: 3 = 43: F	Ex	m	37	m	4	—	0	5	6y	—	—	+	+	156	—	+	—	+	—	—	—	
43: 1p	Ex	f	7	s	2	—	0	4	1d	sl	sl	sl	—	103	+	+	+	+	—	—	—	
43: 2p	Ex	f	1	s	2	—	0	3	1d	sl	—	—	+	73	+	+	—	+	—	—	—	
44: M	Ex	f	56	m	6	*	0	2	10y	—	sl	—	+	149	?	+	+	+	+	sl	49	
44: 1p	Ex	f	29	s	2	—	0	1	8y	—	—	+	—	152	?	+	—	+	—	—	—	
45: M	R	f	55†	m	*	*	*	*	*	*	*	*	*	*	*	*	*	+	*	*	*	
45: 1p	H	m	67†	s	3	—	*	>5	6y	+	+	+	*	*	*	*	*	+	*	*	*	
46: M	Ex	f	48	m	5	*	0	1	6y	—	—	—	—	156	?	+	—	+	—	—	—	
46: 1p	Ex	m	16	s	2	—	sl	4	4y	sl	sl	+	—	161	?	+	—	+	—	—	—	
47: M	R	f	67	m	*	*	*	3	*	*	*	*	*	*	*	*	*	+	*	*	*	
47: 1p	Ex	f	47	m	3	—	0	5	2y	—	—	—	—	156	—	+	+	+	+	—	—	
48: Fp	Ex	m	37	m	3	—	0	12	3y	—	—	+	—	167	—	+	+	+	+	—	—	
48: 1p	Ex	m	11	s	2	—	0	15	1½y	—	—	—	—	144	—	+	-	+	-	..	..	
48: 2p	Ex	f	6	s	2	—	0	6	1½y	—	—	+	—	120		+	—	+	—	..	—	
49: 1 = 50: M	Ex	f	51	m	6	*	0	2	26y	—	—	+	—	161	?	+	—	+	+	—	—	
50: 1	Ex	f	20	s	2	—	0	4	7y	—	—	—	—	156	?	+	—	+	—	—	.	
50: 2p	Ex	m	15	s	2	—	0	6	6y	sl	—	—	—	160	?	—	-	+	—	—	.	

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1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
51: M	Ex	f	42	m	8	*	0	0	—	—	—	—	—	142	—	—	—	+	—	—	—	
51: 1p	Ex	m	22	s	3	—	f	14	1y	s	—	—	+	150	+	+	+	+	—	—	—	
51: 3	Ex	f	9	s	3	—	0	2	2½y	sl	—	—	—	*	—	+	—	+	—	—	—	
52: F	Ex	m	38	m	1	*	0	1	12y	—	—	+	—	161	—	+	+	+	+	s	*	Deafness of left ear.
52: 1p	Ex	m	13	s	2	—	0	2	5y	—	—	—	—	140	+	+	—	+	—	—	—	
53: Mp	Ex	f	44	m	4	*	0	3	7y	—	sl	+	—	160	—	+	—	+	—	sl	31	
53: 1	Ex	m	8	s	1	—	0	1	4y	—	—	—	—	133	—	+	—	+	—	—	—	
54: F	R	m	48†	m	*	*	*	*	*	*	*	*	*	*	*	*	*	+	*	*	*	
54: 3p	Ex	f	41	w	10	—	0	4	6y	—	sl	+	—	155	—	+	—	+	—	sl	28	Fenestration operation.
54: 4p	Ex	m	38	s	10	—	sl	25	5y	sl	sl	+	—	*	?	—	—	+	+	v	10	
54: 7	Ex	m	31	s	10	—	sl	4	13y	sl	—	+	—	159	?	—	—	+	+	sl	29	Deafness of left ear.
55: M	R	f	60†	m	4	*	*	*	*	*	*	*	*	*	*	*	*	+	*	*	*	
55: 2	Ex	m	42	d	5	—	0	1	15y	—	sl	+	+	166	—	+	+	+	—	s	38	
55: 5	Ex	m	36	s	5	—	0	4	2y	—	—	+	—	162	—	+	+	+	+	sl	23	
55: 4 = 56:Mp	Ex	f	38	m	5	—	0	3	4y	sl	—	+	—	149	—	—	+	+	—	—	—	
56: 1	Ex	f	10	s	2	—	0	0	—	—	—	—	—	139	—	—	+	+	—	—	—	
56: 2	Ex	m	7	s	2	—	0	1	6y	—	—	—	—	120	—	—	+	+	—	—	—	
58: M	R	f	*†	m	*	*	*	+	*	*	*	*	*	*	*	*	*	+	*	*	*	

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
58: 3 = 59: M	R	f	75†	m	6?	—	*	*	*	*	*	*	*	*	*	*	*	+	*	*	*	»Small and shrunken.»
58: 6 = 60: M	R	f	62†	m	6?	—	*	+	*	*	*	*	*	*	*	*	*	+	*	*	*	»Small and shrunken.»
59: 2 = 61: F	R	m	72†	m	5	—	0	+	*	*	*	*	*	*	*	*	*	+	*	+	*	
59: 4 = 62: F	R	m	76†	m	5	—	0	+	*	*	*	*	*	*	*	*	*	+	*	+	*	»Small and shrunken.»
59: 5 = 63: F	R	m	53†	m	5	—	0	+	*	*	*	*	*	*	*	*	*	+	*	+	*	»Small and shrunken.»
60: 1	R	f	89†	s	4	—	0	+	*	*	*	*	*	*	*	*	*	+	*	v	*	»Small and shrunken.»
60: 2	R	f	49†	s	4	—	0	+	*	*	*	*	*	*	*	*	*	+	*	*	*	
60: 3 = 64: M	R	f	59†	m	4	—	0	*	*	*	*	*	*	*	*	*	*	+	*	+	*	»Short in stature.»
61: 1 = 65: F	R	m	68†	m	5	—	0	+	*	*	*	*	*	*	*	*	*	+	*	*	*	
61: 2	Ex	m	70	s	5	—	sl	3	49y	sl	s	+	—	152	—	—	—	+	+	—	—	
61: 4 = 66: F	R	m	63†	m	5	—	0	+	*	*	*	*	*	*	*	*	*	+	*	*	*	
62: 1 = 67: F	R	m	61†	m	6	—	0	>3	*	*	*	*	*	*	*	*	*	+	*	*	*	
62: 2	Ex	f	61	s	6	—	0	4	2y	—	—	—	—	152	?	+	—	+	+			History of otitis and deafness.
62: 3	Ex	f	61	s	6	—	sl	6	*	—	sl	+	—	152	?	+	—	+	+	s	38	
63: 1 = 68: M	Ex	f	64	w	10	—	sl	3	*	—	sl	+	+	142	?	—	+	+	+	sl	60	
63: 3	R	m	40†	s	10	—	0	+	*	*	*	*	*	*	*	*	*	+	*	*	*	
63: 4 = 69: M	Ex	f	60	m	10	—	0	3	41y	—	—	+	—	150	—	—	—	+	+	—	—	Deafness of left ear after lesion of ear-drum.
63: 6 = 70: Mp	Ex	f	56	w	10	—	0	1	43y	—	—	+	—	151	?	—	—	+	+			

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
64: 2	R	f	27†	s	7	-	0	*	*	*	*	*	*	*	*	*	*	+	*	*	*	
64: 3 = 71: F	Ex	m	56	m	7	-	0	4	14½y	—	sl	!	-	164	-	—	+	+	+	v	50	
64: 5	Ex	f	53	s	7	-	sl	3	1y	sl	—	—	—	139	—	—	+	+	+	—	—	
64: 7	Ex	f	48	m	7	-	0	5	1d	sl	—	—	—	166	—	+	+	+	+	—	—	
65: 1	Ex	f	41	m	3	—	0	2	2y	—	sl	+	—	159	?	+	—	+	+	—	—	
65: 2	H	f	35†	s	3	-	s	10	*	*	+	+	*	*	*	*	*	+	+	*	*	
66: 2 = 72: M	Ex	f	31	m	5	—	0	1	4y	—	—	+	—	160	?	+	+	+	+	—	—	
66: 3	Ex	f	28	m	5		0	2	3y	sl	—	—	—	143	+	+	+	+	+	—	—	
66: 4	Ex	m	22	s	5	—	0	5	6y	—	—	—	—	168	—	—	—	+	—	—	—	
66: 5	Ex	f	22	s	5		0	5	10y	sl	—	—	—	162	—	+	+	+	—			History of otitis and deafness.
67: 2p	Ex	f	30	s	7		0	4	2y	—	sl	—	—	150	?	—	—	+	—	-		
67: 4p	Ex	m	24	m	7	—	0	10	1y	—	—	—	—	172	—	—	—	+	—	—	—	
67: 5	Ex	m	21	s	7	—	0	3	*	—	-	+	—	182	+	—	—	+	—	—	—	
67: 6p	Ex	f	15	s	7	—	0	2	2y	—	—	+	—	154	—	—	—	+	—	—	—	
67: 7p	Ex	m	12	s	7		0	3	3y	—	—	+	—	139	—	—	—	+	—	—	—	
69: 2 = 73: F	Ex	m	33	m	3	—	0	4	10y	—	—	+	—	178	—	+	—	+	+	—	—	
69: 3	Ex	m	25	s	3	—	0	1	15y	—	—	—	—	178	-	—	—	+	—	—	—	
70: 1	Ex	m	36	m	3	-	sl	6	1y	sl	sl	+	—	167	?	—	+	+	+	—	-	
71: 1	Ex	m	30	m	4	—	f	30	4y	m	—	—	—	160	—	+	+	+	+	—	—	
71: 2	Ex	m	30	s	4	—	0	8	6y	—	—	—	—	186	—	—	+	+	+	sl	19	
72: 1p	Ex	f	5	s	1	-	0	2	1y	—	—	—	—	109	—	—	—	+	—	—	—	
73: 1	Ex	f	4	s	1	-	0	1	10d	—	—	—	—	*	—	—	+	+	—	—	—	
74: 3	Ex	f	2	s	3	—	0	0	—	—	—	—	-	*	—	—	+	+	—	—	—	
75: M	R	f	40†	m	*	*	0	*	*	*	*	*	*	*	*	*	*	+	*	*	*	

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
75: 1 = 76: F	Ex	m	61	m	9	—	0	5	4y	sl	—	+	—	178	—	—	—	+	+	—	—	
75: 3 = 77: F	Ex	m	58	m	9	—	0	6	2y	sl	sl	—	—	176	—	—	—	+	+	s	49	
75: 5	Ex	m	54	s	9	—	0	2	15y	sl	—	+	—	182	—	—	—	+	—	s	40	
75: 6 = 78: M	R	f	45†	m	9	—	0	*	*	*	*	*	*	*	*	*	*	+	*	*	*	
75: 8 = 79: F	Ex	m	46	m	9	—	9	4	6y	—	—	+	—	178	—	+	—	+	—	—	—	
75: 9 = 80: M	Ex	f	44	m	9	—	0	0	—	—	—	—	—	160	—	+	—	+	—	—	—	
76: 3	Ex	f	30	s	5	—	0	5	1y	—	—	—	—	159	—	+	+	+	+	—	—	
77: 1	Ex	f	35	m	2	—	0	1	11y	—	sl	+	—	163	?	+	—	+	—	—	—	
77: 2p	Ex	f	26	s	2	—	0	9	1y	—	—	+	—	170	—	+	—	+	—	—	—	
78: 1	Ex	f	33	m	4	—	0	6	2y	sl	sl	+	—	162	—	+	—	+	—	sl	29	
78: 4p	Ex	m	15	s	4	—	0	6	3y	sl	sl	—	—	168	—	+	—	+	—	—	—	
79: 1p	Ex	m	14	s	1	—	0	8	2y	sl	—	+	—	168	—	+	—	+	—	—	—	
80: 2	Ex	m	19	s	2	—	0	12	1y	—	—	+	—	168	—	+	—	+	—	—	—	
81: Fp	Ex	m	70	m	5	*	0	4	*	sl	sl	+	—	*	—	+	—	+	+			History of otitis and deafness.
81: 1	Ex	m	39	s	4	—	f	8	1y	s	—	—	—	*	—	+	—	+	—	—	—	
81: 2	Ex	m	36	s	4	—	0	1	8y	—	sl	—	—	166	—	+	—	+	—	—	—	
81: 4	Ex	m	23	s	4	—	0	3	2y	—	—	—	—	173	—	+	—	+	—	—	—	
82: 3 = 83: F	R	m	65†	m	8	—	0	+	*	*	*	*	*	*	*	*	*	*	*	*	*	
82: 6 = 84: F	R	m	73†	m	8	—	0	+	*	*	*	*	*	*	*	*	*	*	*	*	*	
83: 2 = 85: F	Ex	m	52	m	3	—	0	3	3y	sl	sl	+	—	164	—	—	—	—	—	—	—	
84: 1 = 86: F	Ex	m	49	m	2	—	0	12	1y	sl	sl	—	—	160	—	—	+	—	—	—	—	
84: 2	Ex	m	42	m	2	—	0	4	7y	sl	sl	+	—	180	—	—	—	—	—	—	—	
85: 1	Ex	m	22	s	2	—	0	6	2y	—	sl	—	—	170	—	—	+	—	—	—	—	

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
86: 1p	Ex	f	17	s	3	—	f	11	7y	s	sl	+	—	150	—	-	-	-	-	-	—	
87: Mp	Ex	f	37	m	5	+	0	4	6y	—	—	+	—	158	—	—	—	+	—	sl	34	
87: 1	Ex	m	14	s	4	—	0	1	12y	sl	—	—	—	157	—	+	+	+	—	—	—	
Sibships with two or more affected with normal parents:																						
94: 2	R	f	13†	s	4	—	s	+	1y	*	*	*	*	*	*	*	*	—	*	*	*	
94: 4p	Ex	f	51	s	4	—	f	35	1y	s	s	+	—	130	?	·	–		—	—	—	
96: 3	R	f	6†	s	7	—	s	+	2y	*	*	*	*	*	*	*	*	*	*	*	*	
96: 4p	Ex	m	40	s	7	—	s	+	2y	s	s	—	—	*	?	+	–	–	-	–	–	
96: 6p	R	m	17†	s	7	—	s	+	2½y	*	*	*	*	*	*	*	*	*	*	*	*	
97: 1	Ex	f	31	s	6	—	f	12	1y	s	s	—	—	118	+	—	+	—	—	—	—	
97: 4p	Ex	f	24	s	6	—	0	3	2y	—	sl	+	—	139	?	—	—	+	-	—	—	
97: 5	Ex	f	19	m	6	—	0	5	3y	—	—	—	—	159	+	—	—	·	—	sl	10	Deafness of left ear after trauma.
97: 6p	Ex	m	14	s	6	—	s	12	4y	s	sl	—	—	117	?	—	—	+	—	—	—	
Solitary cases:																						
120: 1p	Ex	m	19	s	1	+	sl	13	2y	m	sl	+	+	158	+	+	+	+	+	—	—	Small and shrunken.
121: 4p	Ex	f	13	s	5	+	f	19	1d	s	s	—	+	*	+	+	—	+	—	—	—	
122: 6p	Ex	m	3	s	6	+	0	1	1½y	—	—	—	+	*	+	—	—	+	—	—	—	Deafness of left ear.
123: 1p	Ex	m	16	s	1	+	sl	19	9y	sl	—	—	—	180	—	+	—	+	—	sl	2	

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
124: 1p	Ex	f	15	s	4	+	0	18	9m	sl	–	–	–	155	–	–	–	+	–	–	–	
125: 2p	Ex	m	28	s	5	+	s	21	1y	s	m	–	+	93	+	+	+	–	–	sl	*	Deafness of left ear.
126: 2p	Ex	m	15	s	2	+	0	7	3y	sl	–	–	–	152	–	+	+	+	–	–	–	
127: 8p	Ex	m	25	s	8	+	sl	10	2½y	sl	–	–	–	176	–	–	–	+	–	–	–	
128: 5p	H	m	20†	s	6	+	0	5	2y	*	*	*	*	*	*	*	*	+	*	*	*	
129: 1p	Ex	m	39	s	1	+	f	35	½m	m	–	+	+	157	?	–	+	+	–	–	–	
130: 2p	Ex	m	57	s	5	+	f	15	2y	m	–	–	+	140	?	–	–	–	–	–	–	
131: 3p	H	f	51†	s	6	+	s	+	1d	s	s	*	*	*	*	*	*	*	+	+	*	
132: 7p	Ex	f	51	m	7	+	0	4	9y	sl	–	+	–	153	–	+	–	+	+	sl	37	
133: 2p	Ex	m	23	s	3	+	s	10	1y	s	–	–	–	120	–	+	–	–	–	–	–	
134: 1p	H	f	7†	s	2	+	f	+	1d	+	+	+	+	*	+	*	*	+	*	*	*	
135: 1p	Ex	f	5	s	1	+	s	29	1d	s	–	–	+	86	+	–	+	+	–	–	–	
137: 2p	Ex	f	23	s	2	+	0	6	12y	–	sl	+	–	150	–	+	+	+	–	–	–	
139: 2p	Ex	m	11	s	1	+	s	50	1y	m	–	+	–	124	–	–	–	–	–	–	–	
140: 1p	Ex	m	13	s	1	+	s	33	1d	s	m	+	+	132	+	–	–	–	–	–	–	
141: 2p	Ex	f	6	s	4	+	s	14	1d	s	s	+	+	80	+	+	+	+	–	–	–	
142: 3p	Ex	f	27	m	7	+	f	20	2½y	m	sl	+	–	151	–	+	+	+	–	sl	20	
143: 2p	Ex	f	34	s	4	+	s	11	4y	s	s	+	+	120	?	+	+	+	+	sl	5	
145: 2p	Ex	f	14	s	3	+	0	9	2y	–	sl	+	–	157	+	–	+	+	–	–	–	
146: 1p	Ex	f	9	s	1	+	sl	5	11m	m	m	+	+	102	?	+	+	+	–	–	–	
147: 1p	Ex	m	6	s	1	+	s	10	1d	s	–	–	+	105	+	–	+	–	–	–	–	
148: 5p	Ex	f	6	s	6	+	0	6	15m	sl	–	+	+	105	?	+	–	+	–	–	–	
149: 1p	Ex	m	5	s	1	+	sl	7	3m	sl	–	–	–	*	?	–	+	–	–	–	–	
150: 2p	Ex	m	36	m	2	+	s	40	2y	s	s	+	–	*	+	+	–	–	–	–	–	
151: 4p	Ex	m	15	s	5	+	s	40	1d	s	–	+	–	150	–	+	–	+	–	–	–	

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
152: 4p	Ex	f	46	s	7	+	s	10	1½y	s	m	+	+	115	+	+	–	+	–			History of otitis and deafness.
153: 2p	Ex	m	12	s	3	+	f	7	13m	m	m	+	+	123	+	+	+	+	–	–	–	
154: 5p	Ex	m	37	s	6	+	f	25	½y	m	s	+	+	109	–	–	+	+	–	sl	20	
155: 2p	Ex	f	26	s	3	+	s	19	12y	sl	s	+	–	134	–	+	+	–	–	–	–	Of foreign birth.
156: 2p	Ex	f	11	s	2	+	0	4	1½y	–	–	–	–	140	–	+	+	+	–	–	–	
157: 1p	Ex	f	9	s	2	+	0	4	1d	–	–	–	–	*	–	–	–	–	–	–	–	
158: 2p	Ex	m	17	s	2	+	sl	10	6y	sl	–	–	+	152	+	+	+	+	–			History of otitis and deafness.
159- 6p	Ex	f	24	s	5	+	s	125	4y	s	m	+	–	124	–	+	+	–	–	–	–	
160: 2p	Ex	m	49	m	4	+	f	21	2y	s	sl	–	–	140	–	–	+	–	–	–	–	
161: 6p	Ex	f	48	s	8	+	s	+	*	s	s	+	–	67	+	+	–	+	–			History of otitis and deafness.
162: 7p	H	m	57†	m	10	+	sl	+	*	*	*	*	*	*	*	*	*	*	*	*	*	
163: 1p	H	f	1	s	1	*	*	+	1y	*	*	*	*	*	*	*	*	+	*	*	*	Of foreign birth. Emigrated 1953.
164: 1p	Ex	f	15	s	1	+	0	8	1y	–	sl	+	–	167	+	–	–	–	–	–	–	
165: 2p	Ex	m	15	s	2	+	f	26	3d	m	m	+	–	*	+	–	–	–	–	–	–	
166: 1p	H	m	48†	m	1	+	0	3	*	sl	*	+	*	*	*	*	*	+	*	+	*	
167: 2p	Ex	m	4	s	2	+	sl	4	1y	–	–	–	–	*	–	+	+	+	–	–	–	
168: 3p	Ex	m	30	s	3	+	s	20	1y	s	s	–	+	112	–	–	+	–	–	–	–	
169: 2p	Ex	m	13	s	2	+	0	26	1½y	sl	–	–	–	164	–	–	–	+	–	–	–	
170: 1p	Ex	m	27	s	2	+	s	50	½y	s	sl	–	–	135	–	+	–	+	–	–	–	
171: 5p	Ex	m	60	s	8	+	f	19	1½m	s	s	+	+	136	–	+	–	–	–			History of otitis and deafness.
172: 1p	Ex	m	19	s	1	+	0	11	2y	–	sl	+	–	174	–	+	–	+	–	–	–	
173: 1p	Ex	f	26	m	2	+	0	13	2m	sl	–	–	–	157	–	+	+	+	–	–	–	Of foreign birth.
174: 1p	Ex	m	7	s	1	+	s	12	1d	m	m	–	+	*	?	+	–	+	–	–	–	Of foreign birth.

TABLE 64. *Lethal cases (Osteogenesis imperfecta congenita).*

Identification number	Information H — Hospital record	sex m = male f = female	Age at death	Total number of children in this sibship	Sporadic case	Fracture	Deformities	Age at which fractures and/or deformities were observed	Disturbed ossification of cranial bones	Blue sclerotics	Arcus corneae	Arteriosclerotic changes of blood vessels
1	2	3	4	5	6	7	8	9	10	11	12	13
	Sibships with 2—3 affected with normal parents:											
95: 3p	H	m	2½m	7	—	+	s	B	+	+	*	*
95: 4p	H	m	5½m	7	—	+	s	B	+	+	*	*
95: 6p	H	m	12½m	7	—	+	s	B	+	+	*	*
98: 1p	H	f	13½m	2	—	+	s	B	+	*	*	*
98: 2p	H	m	9½m	2	—	+	s	B	+	*	*	*
	Solitary (lethal) cases:											
100: 3p	H	m	3m	5	+	+	s	B	+	+	*	+
101: 7p	H	f	1m	1	+	+	s	B	+	—	*	*
102: 4p	H	m	8½m	4	+	+	+	B	+	*	*	*
103: 1p	H	f	s. p.	3	+	+	*	B	*	*	*	*
104: 2p	H	f	15½m	2	+	+	s	B	+	+	*	*
105: 1p	H	m	16d	2	+	+	s	B	+	*	*	*
106: 6p	H	m	i. u.	7	+	+	s	B	*	*	*	*
107: 4p	H	f	3m	4	+	+	s	B	*	*	*	*
108: 3p	H	f	s. p.	4	+	+	m	B	+	*	*	*
110: 2p	H	m	3d	3	+	+	s	B	+	*	*	*
111: 5p	H	m	9½m	5	+	+	s	B	—	*	*	*
112: 2p	H	f	1m	3	+	+	s	B	+	*	*	*
113: 2p	H	f	1d	5	+	+	s	B	*	*	*	*
114: 1p	H	f	1d	2	+	+	m	B	+	*	*	*
115: 3p	H	f	2y 7m	6	+	+	s	10d?	+	+	*	*
116: 5p	H	f	10m	5	+	+	s	B	+	+	*	*
117: 2p	H	m	11m	2	+	+	s	B	+	+	+	*

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